



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 33

A. R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 33

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

The present volume consists of five chapters, three of which are on subjects previously covered in these advances.

The photochemistry of oxygen- and sulfur-containing heterocycles is complementary to the review on the photochemistry of nitrogen heterocycles that appeared in Volume 30; together these two chapters update an earlier review of the photochemistry of heterocycles (all by S. T. Reid), which appeared in 1970 in Volume 11. Paudler and Sheets have updated their review of the general chemistry of naphthyridines, which also appeared in Volume 11. In addition, van der Plas, Wózniak, and van den Haak have specifically considered the reactions of naphthyridines with nitrogen nucleophiles, largely from their own extensive investigations in this area.

Hermecz and Mészáros have surveyed the chemistry of pyrido[1,2-*a*]pyrimidines (and have included 469 references). The only earlier review that covers the literature up to 1957 listed a mere 43 references. Finally, Timpe and El'tsov have dealt with the enormous subject of pseudoazulenes, defined in a broad way to cover a wide variety of bicyclic heterocycles.

A. R. KATRITZKY

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The Photochemistry of Oxygen- and Sulfur-Containing Heterocycles

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Canterbury, Kent, England*

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I. Introduction

Recent advances in the photochemistry of nitrogen-containing heterocycles have been reviewed in Volume 30 of this series.¹ This review is intended to update an earlier review on the photochemistry of heterocycles² with

¹ S. T. Reid, *Adv. Heterocycl. Chem.* 30, 239 (1982).

² S. T. Reid, *Adv. Heterocycl. Chem.* 11, 1 (1970).

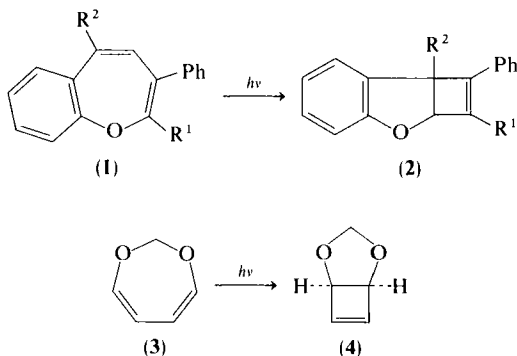
respect to oxygen- and sulfur-containing systems and covers the period from 1969 to June 1981. The arrangement of material is essentially identical to that adopted for the review on nitrogen-containing heterocycles; this should facilitate cross reference between the systems. This survey is necessarily selective rather than comprehensive in its coverage.

II. Bond Cleavage and Rearrangement

A. ELECTROCYCLIC REACTIONS

1. 4π Systems

Examples of 4π electrocyclization and related ring openings in oxygen- and sulfur-containing heterocycles have been widely reported. The effect of substituents on the ease of photocyclization of 1-benzoxepins (**1**) to cyclobuta[*b*]-1-benzofurans (**2**) has been studied.³ 1,3-Dioxepin (**3**) is readily converted to 2,4-dioxabicyclo[3.2.0]hept-6-ene (**4**) on irradiation in diethyl



ether,⁴ and similar transformations have been reported in 3-phenyl-2(3*H*)-oxepinones⁵ and in 8-oxabicyclo[5.1.0]octa-2,4-diene.⁶ α -Pyrone (**5**) is

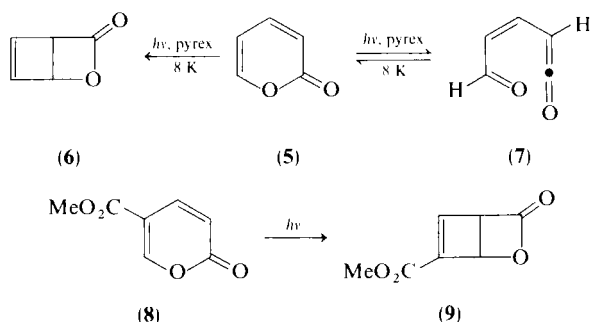
³ H. Hofmann and P. Hofmann, *Justus Liebigs Ann. Chem.*, 1597 (1977).

⁴ J. F. W. Keana and R. H. Morse, *Tetrahedron Lett.*, 2113 (1976).

⁵ K. Sato, H. Hagiwara, H. Uda, M. Sato, and N. Harada, *J. Am. Chem. Soc.* **98**, 8281 (1976).

⁶ P. Schiess and M. Wisson, *Helv. Chim. Acta* **57**, 1692 (1974).

known to undergo photoisomerization to the β -lactone (6) at -20°C ⁷; reinvestigation of this transformation in an argon matrix at 8 K led to the formation in high yield of the β -lactone, which was subsequently used as a precursor of cyclobutadiene.⁸ Further detailed investigations of this photoisomerization have shown that competing but reversible formation of four rotamers of the aldehyde (7) exists, arising presumably by an electrocyclic ring-opening pathway.⁹ Similar approaches have been employed in the syntheses of the tricarbonyliron complex of cyclobutadienecarboxylic acid,¹⁰ mono-, and dideuterocyclobutadienes,¹¹ and [^{13}C]cyclobutadiene¹²; methyl coumalate (8) is readily converted to the bicyclic lactone (9) on irradiation in diethyl ether.¹³



6-Acetoxy-1,4-dithiocin (10), like benzo-1,4-dithiocin, is converted on irradiation to the bicyclic isomer (11).¹⁴ Analogous cyclizations have been observed in certain 4-phenyl-1-benzothiepins (12)¹⁵ and in 1-benzothiepin itself.¹⁶ Further rearrangement of the photoproduct (13) to isomer 14 is believed to occur via the diradical intermediate (15).

⁷ E. J. Corey and J. Streith, *J. Am. Chem. Soc.* **86**, 950 (1964).

⁸ O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.* **95**, 614 (1973).

⁹ O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.* **95**, 244 (1973); R. G. S. Pong and J. S. Shirk, *ibid.*, 248.

¹⁰ J. Agar, F. Kaplan, and B. W. Roberts, *J. Org. Chem.* **39**, 3451 (1974).

¹¹ O. L. Chapman, D. De La Cruz, R. Roth, and J. Pacansky, *J. Am. Chem. Soc.* **95**, 1337 (1973).

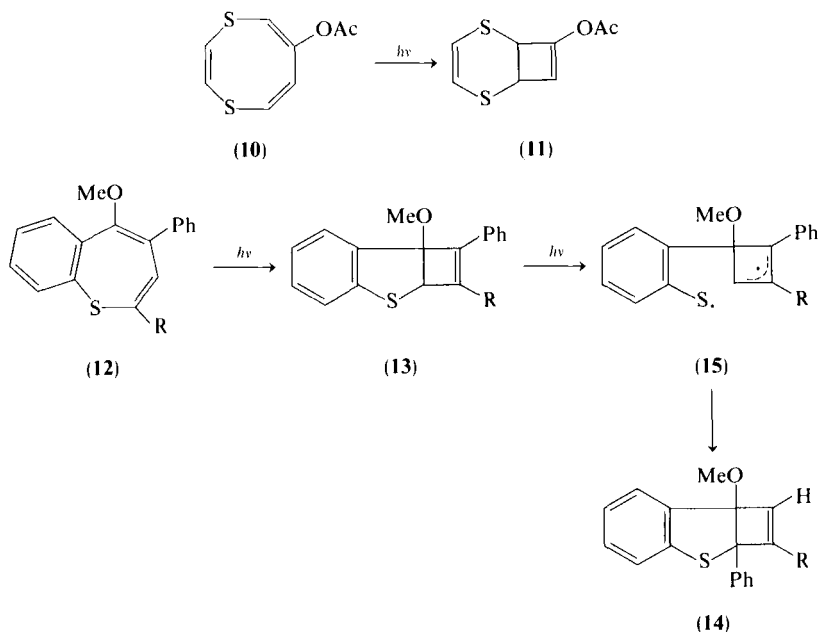
¹² R. G. S. Pong, B.-S. Huang, J. Laurenzi, and A. Krantz, *J. Am. Chem. Soc.* **99**, 4153 (1977).

¹³ H. Javaheripour and D. C. Neckers, *J. Org. Chem.* **42**, 1844 (1977).

¹⁴ H. J. Eggette, F. Bickelhaupt, and B. O. Loopstra, *Tetrahedron* **34**, 3631 (1978).

¹⁵ H. Hofmann and H. Gaube, *Justus Liebigs Ann. Chem.*, 1874 (1977).

¹⁶ I. Murata, T. Taksuoka, and Y. Sugihara, *Angew. Chem., Int. Ed. Engl.* **13**, 142 (1974).



2. 6π Systems

Examples of photochemically induced 6π electrocyclizations in oxygen-containing systems are relatively rare. 2*H*-Phenanthro[9,10-*b*]-pyran-4-carboxamides (**16**), for example, have been obtained in this way by irradiation of dienones (**17**).¹⁷ Similarly, the α -pyran (**18**) is formed on irradiation of (*E*)- β -ionone (**19**)¹⁸; a triplet excited state is believed to be involved and the reaction proceeds via the *Z*-isomer (**20**). The reverse process involving ring opening is more common and can lead to a wide variety of photochemically derived products. Thus, the products of irradiation of 2,2-dimethylchromene (**21**) can easily be rationalized in terms of initial formation of *o*-quinoneallide (**22**).¹⁹ An analogous ring cleavage has been reported in 6,6-dimethyldibenzo[*b,d*]pyran.²⁰ A more complex sequence of reactions has been observed for 4-carbomethoxy-3-chromanone (**23**) and the proposed pathway is outlined in Scheme 1.²¹ 1,5-Hydrogen migration occurs readily in the

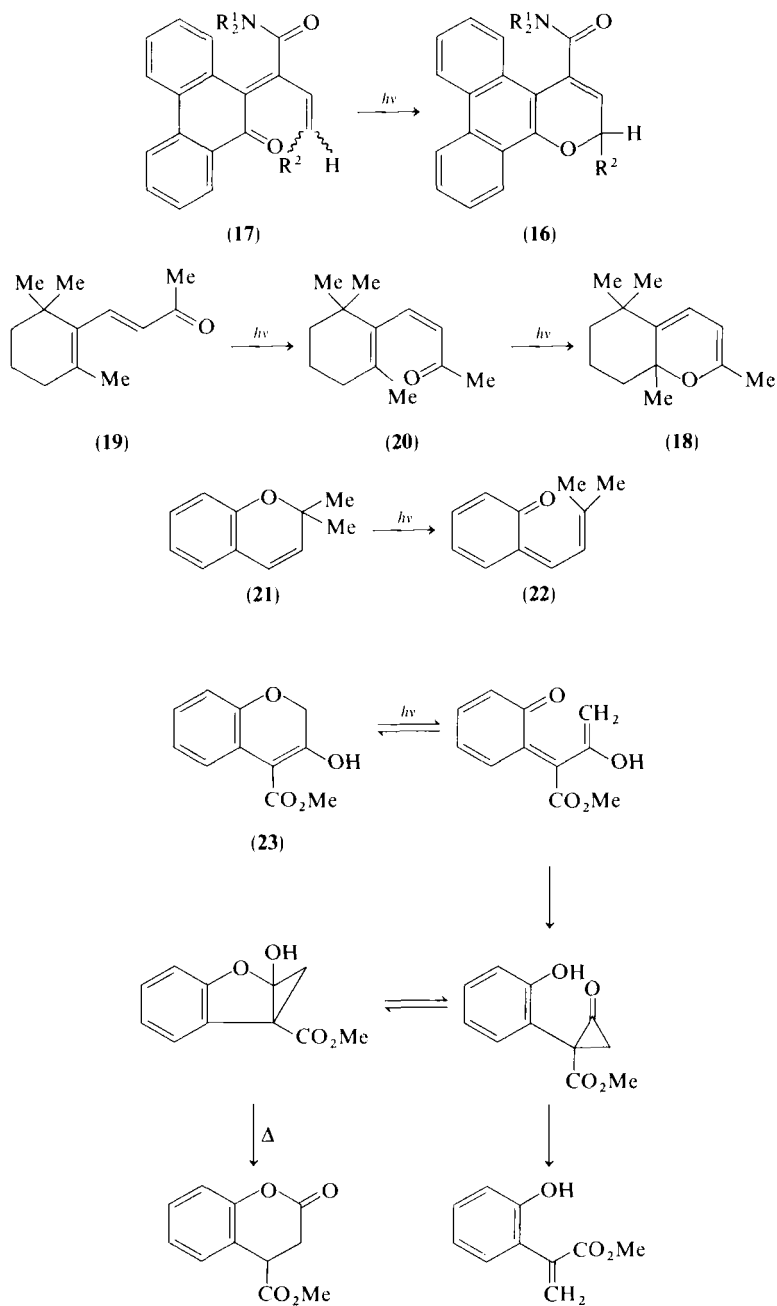
¹⁷ W. Verboom, A. V. E. George, L. Brandsma, and H. J. T. Bos, *Recl. Trav. Chim. Pays-Bas* **99**, 29 (1980).

¹⁸ A. Van Wageningen, H. Cerfontain, and J. A. J. Geenevasen, *J. C. S. Perkin II*, 1283 (1975); H. Cerfontain, J. A. J. Geenevasen, and P. C. M. Van Noort, *ibid.*, 1057 (1980).

¹⁹ A. Padwa, A. Au, G. A. Lee, and W. Owens, *J. Org. Chem.* **40**, 1142 (1975).

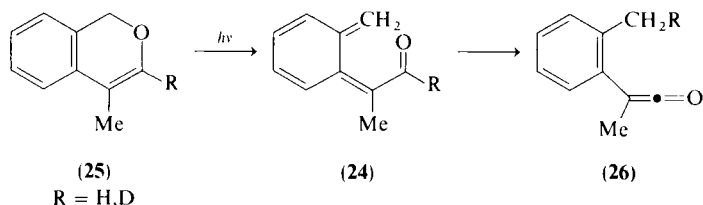
²⁰ A. Bowd, J. H. Turnbull, and J. D. Coyle, *J. Chem. Res., Synop.*, 202 (1980).

²¹ A. Padwa and A. Au, *J. Am. Chem. Soc.* **97**, 242 (1975).

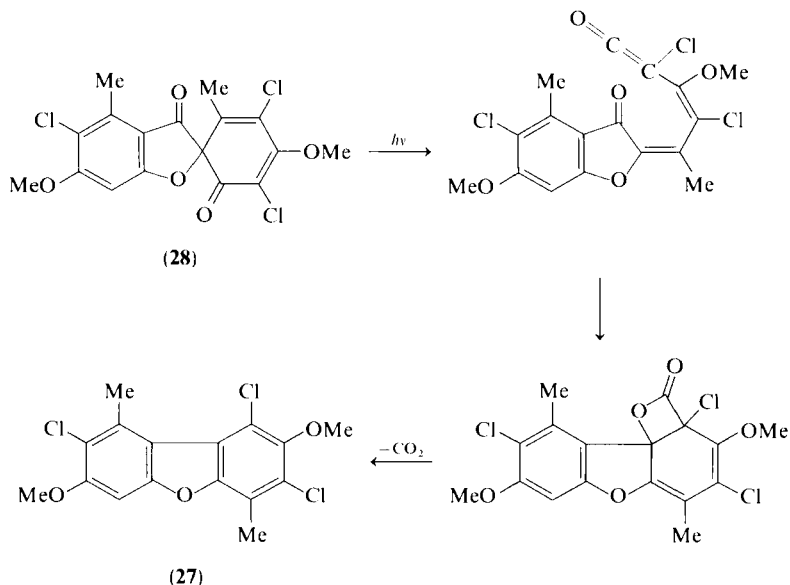


SCHEME 1

o-xylylene (**24**) ($R = H$), obtained by irradiation of 4-methylisochromene (**25**), to give the ketene (**26**)²²; attempts to trap the *o*-xylylene with dienophiles have been unsuccessful. Analogous photochemically induced ring openings in benzoindolinospiropyrans, widely studied for possible application in imaging systems, are responsible for their photochromic properties.²³



Synthesis of the dibenzofuran (**27**) by irradiation of grise-3',5'-diene-2',3'-dione (**28**) is believed to involve electrocyclic ring opening followed by intramolecular cycloaddition to the ketene and elimination of carbon dioxide, as shown in Scheme 2.²⁴ Analogous photocyclizations are responsible for the photochromism exhibited by heterocyclic fulgides such as (*E*)- α -3-furyl-ethylidene(isopropylidene)succinic anhydride (**29**), which on irradiation



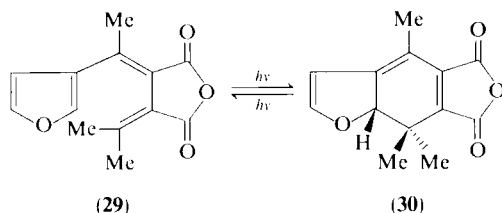
SCHEME 2

²² J. M. Hornback and B. Vadlamani, *J. Org. Chem.* **45**, 3524 (1980).

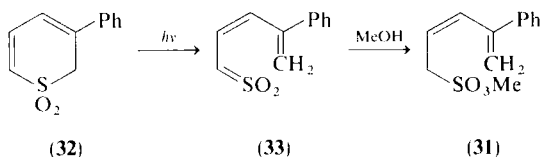
²³ R. E. Jacobson, *Chem. Br.* **16**, 468 (1980); G. A. Delzenne, *Adv. Photochem.* **11**, 1 (1979).

²⁴ T. Sala and M. V. Sargent, *J. C. S. Perkin I*, 870 (1981).

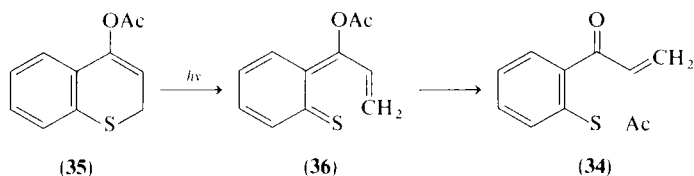
undergoes conrotatory ring closure to give the red-colored dihydrobenzo-[*b*]furan (30) in nearly quantitative yield.²⁵



Certain thiin derivatives undergo similar transformations. The formation of the sulfonate ester (31) on irradiation of 3-phenyl-2*H*-thiopyran 1,1-dioxide (32) in methanol strongly supports the intermediacy of the sulfene (33).²⁶ Initial formation of a sulfene has also been proposed to account for



the photoreactions of 2*H*-1-benzothiopyran 1,1-dioxide,²⁷ and the formation of 1-(2-acetylthiophenyl)propen-1-one (34) on irradiation of the enol acetate (35) in acetonitrile is regarded as arising by electrocyclic ring opening to the thione (36), followed by a novel 1,5-acyl migration.²⁸



Numerous examples of stilbene-to-dihydrophenanthrene photocyclization incorporating oxygen and sulfur heterocycles have been reported. Oxidation to the phenanthrene is usually effected by added iodine or by oxygen. Thus, irradiation of 2,3-diphenylchromone (37) results in the formation of phenanthro[9',10'-2,3]chromone (38)²⁹; analogous photocyclizations have

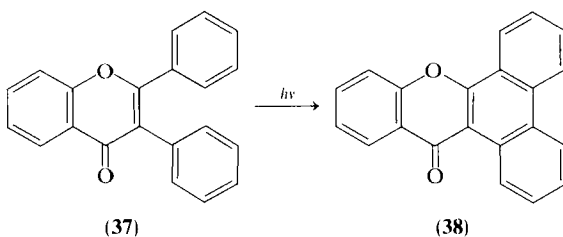
²⁵ H. G. Heller and S. Oliver, *J. C. S. Perkin I*, 197 (1981).

²⁶ J. F. King, E. G. Lewars, D. R. K. Harding, and R. M. Enanoza, *Can. J. Chem.* **53**, 3657 (1975).

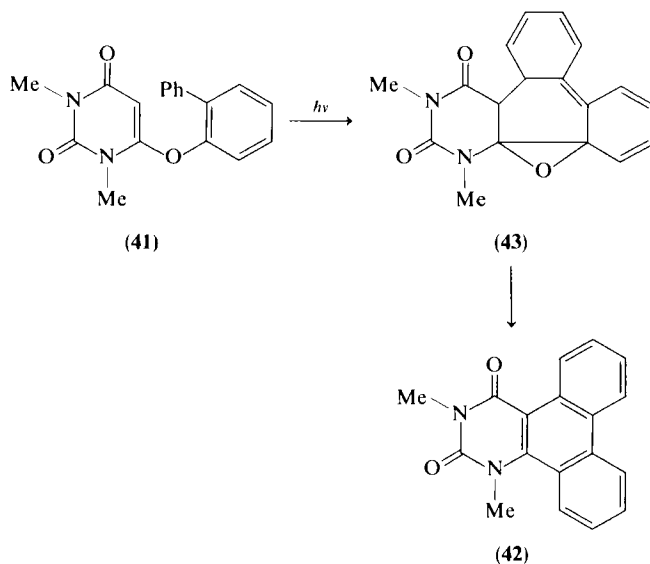
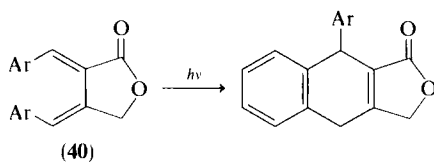
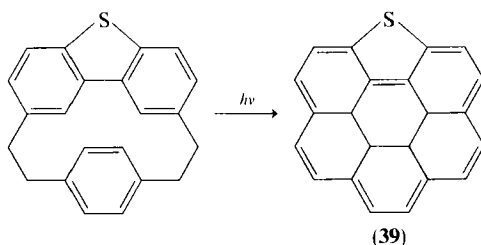
²⁷ C. R. Hall and D. J. H. Smith, *Tetrahedron Lett.*, 3633 (1974).

²⁸ I. W. J. Still and T. S. Leong, *Tetrahedron Lett.*, 3613 (1979).

²⁹ K. L. Prasunamba, G. Srimannarayana, and N. V. Subba Rao, *Indian J. Chem., Sect. B* **15B**, 756 (1977).



been reported for, among others, 2,3-diphenylbenzo[*b*]furan,³⁰ 9-benzylidenexanthenes and 9-benzylidenethioxanthenes,³¹ 1,2-diarylvinylidene

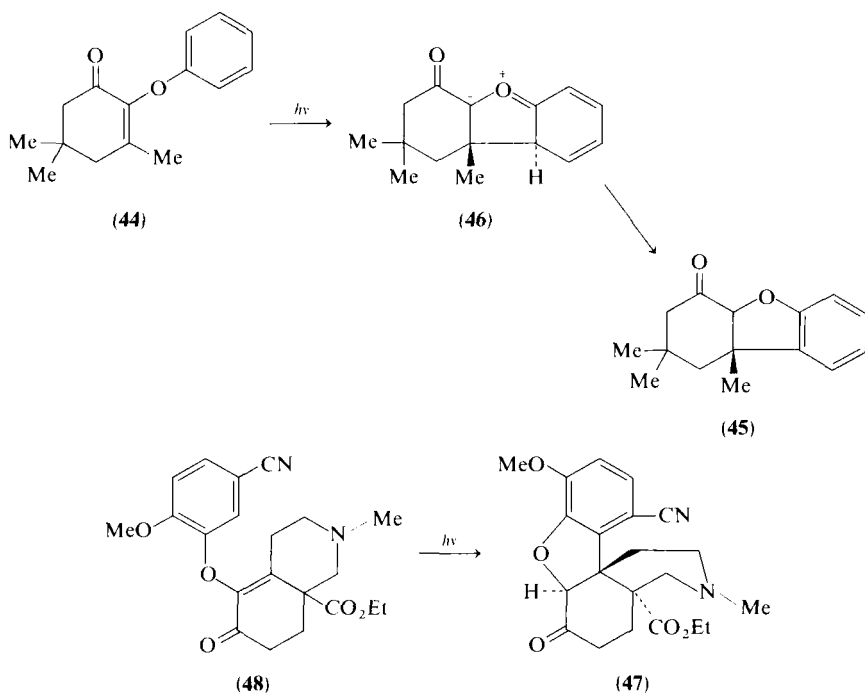


³⁰ A. Couture, A. Lablache-Combier, and H. Offenber, *Tetrahedron* **31**, 2023 (1975).

³¹ A. Schönberg and M. M. Sidky, *Chem. Ber.* **107**, 1207 (1974).

carbonates,³² 2,3,11,12-tetraphenyl-2,3,11,12-didehydro-18-crown-6,³³ and 1-(benzothien-3-yl)-2-(1-naphthyl)ethylene.³⁴ New thiophen-containing heterohelicenes³⁵ and bridged [18]annulene (39), which upon exposure to air is further converted to thiacoronene,³⁶ have also been synthesized in this way. The related photocyclization of 2,3-dibenzylidenebutylolactones (40)³⁷ has been widely used in the synthesis of apolignans.³⁸ Similarly, the photocyclodehydration of 6-*o*-biphenyloxy-1,3-dimethyluracil (41) to give the fused phenanthrene (42) is believed to proceed via the oxiran (43).³⁹

The process known as "heteroatom-directed photoarylation" is also believed to involve a conrotatory photocyclization followed by a suprafacial



³² I. Lantos, *Tetrahedron Lett.*, 2761 (1978).

³³ M. Eichner and A. Merz, *Tetrahedron Lett.*, 1315 (1981).

³⁴ A. Croisy, P. Jacquignon, and F. Perin, *J. C. S. Chem. Commun.*, 106 (1975).

³⁵ J. H. Dopper, D. Oudman, and H. Wynberg, *J. Am. Chem. Soc.* **95**, 3692 (1973); P. G. Lehman and H. Wynberg, *Aust. J. Chem.* **27**, 315 (1974).

³⁶ J. Lawson, R. DuVernet, and V. Boekelheide, *J. Am. Chem. Soc.* **95**, 956 (1973).

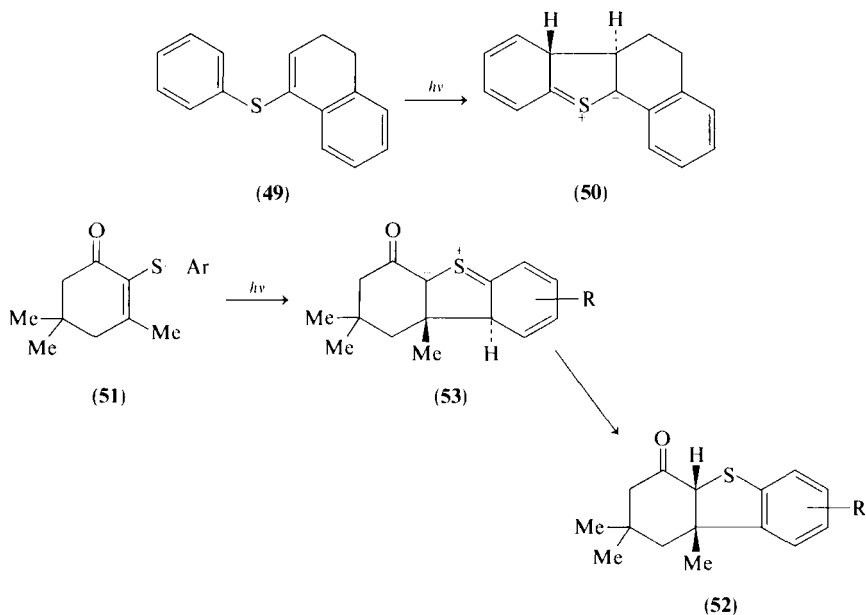
³⁷ H. G. Heller and P. J. Strydom, *J. C. S. Chem. Commun.*, 50 (1976).

³⁸ T. Momose, T. Nakamura, and K. Kanai, *Heterocycles* **6**, 277 (1977); T. Momose, K. Kanai, T. Nakamura, and Y. Kuni, *Chem. Pharm. Bull.* **25**, 2755 (1977); T. Momose, T. Nakamura, and K. Kanai, *ibid.* **26**, 3186 (1978); T. Momose, K. Kanai, and K. Hayashi, *ibid.*, 3195.

³⁹ R. D. Youssefyeh and M. Weisz, *J. Am. Chem. Soc.* **96**, 315 (1974).

1,4-hydrogen migration. Thus, irradiation of the aryloxyenone (**44**) affords the dihydrobenzofuran (**45**) via the intermediate carbonyl ylide (**46**).⁴⁰ A triplet excited state is involved.⁴¹ The stereochemistry of such cyclizations has been investigated,⁴² and the synthesis of a tetracyclic morphine analog (**47**) has been achieved by irradiation of the aryloxyenone (**48**).⁴³

The corresponding photocyclization of *S*-arylvinyl sulfides to dihydrothiophens has been shown to proceed via short-lived thiocarbonyl ylide intermediates, formed in turn by cyclization of triplet excited states. 1-Phenylthio-3,4-dihydronaphthalene (**49**), for example, affords the colored thiocarbonyl ylide (**50**)⁴⁴; the isolated products are derived by processes involving hydrogen abstraction and migration. The greater efficiency of the photocyclization of 2-thioaryloxyenones (**51**) to dihydrothiophens (**52**) has been attributed to the additional stabilization afforded to the ylide (**53**) by the carbonyl group.⁴⁵ Other similar photocyclizations have been reported.⁴⁶



⁴⁰ A. G. Schultz and R. D. Lucci, *J. Org. Chem.* **40**, 1371 (1975).

⁴¹ T. Wolff, *J. Org. Chem.* **46**, 978 (1981).

⁴² A. G. Schultz and W. Y. Fu, *J. Org. Chem.* **41**, 1483 (1976).

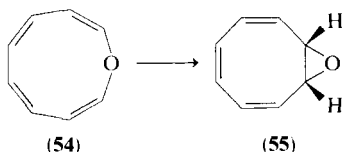
⁴³ A. G. Schultz and R. D. Lucci, *J. C. S. Chem. Commun.*, 925 (1976).

⁴⁴ T. Wolff, *J. Am. Chem. Soc.* **100**, 6157 (1978), *J. Photochem.* **11**, 215 (1979).

⁴⁵ A. G. Schultz, W. Y. Fu, R. D. Lucci, B. G. Kurr, K. M. Lo, and M. Boxer, *J. Am. Chem. Soc.* **100**, 2140 (1978).

⁴⁶ T. Sasaki and K. Hayakawa, *Tetrahedron Lett.*, 1525 (1980); A. G. Schultz and M. B. De Tar, *J. Am. Chem. Soc.* **98**, 3564 (1976).

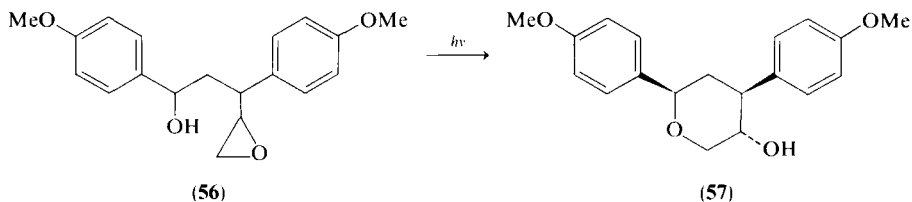
Irradiation of oxonin (**54**) has been shown to lead exclusively to cyclo-octatetraene oxide (**55**) and not to 8,9-dihydrobenzofuran as originally proposed.⁴⁷



B. MISCELLANEOUS REACTIONS

1. Three- and Four-Membered Heterocycles

The photodecomposition of oxiran and alkylloxirans both in the gas phase and in solution has been extensively investigated. Processes arising by carbon-oxygen bond homolysis and hydrogen abstraction have been reported, and the subject has been reviewed in detail elsewhere.⁴⁸ The most recent studies include the photoaddition of methanol to alicyclic epoxides, a process that appears to be promoted by acid,⁴⁹ and the interesting if unusual photochemically induced conversion of the epoxyalcohol (**56**) to sugiresinol dimethyl ether (**57**).⁵⁰



Related photochemical transformations have been reported in unsaturated oxirans. The formation of β,γ -unsaturated ketones (**58**) from the α,β -unsaturated oxirans (**59**) is believed to proceed via hydrogen migration in the allylic radical (**60**).⁵¹ Carbon-oxygen bond homolysis, followed by two

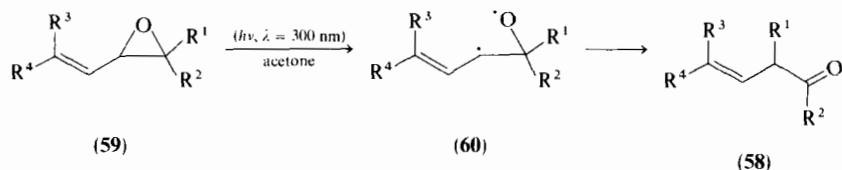
⁴⁷ A. G. Anastassiou and R. P. Cellura, *J. C. S. Chem. Commun.*, 1521 (1969).

⁴⁸ S. Braslavsky and J. Heicklen, *Chem. Rev.* **77**, 473 (1977); N. R. Bertoniere and G. W. Griffin, *Org. Photochem.* **3**, 115 (1973).

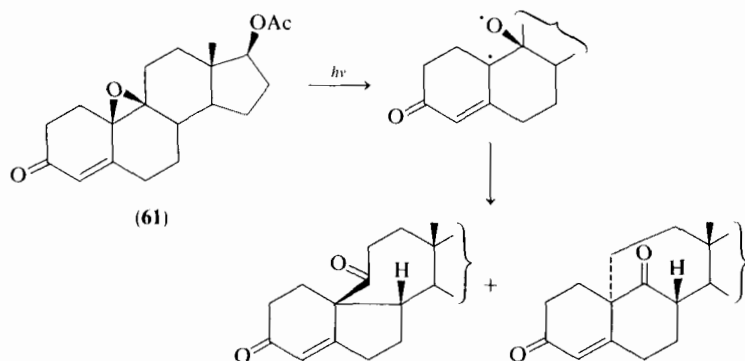
⁴⁹ G. Roussi and R. Beugelmans, *Tetrahedron Lett.*, 1333 (1972); M. Hisaoka and K. Tokumaru, *Chem. Lett.*, 351 (1973).

⁵⁰ Z. Horii, C. Iwata, T. Tanaka, and T. Momose, *Heterocycles* **6**, 697 (1977).

⁵¹ D. R. Paulson, G. Korngold, and G. Jones, *Tetrahedron Lett.*, 1723 (1972).

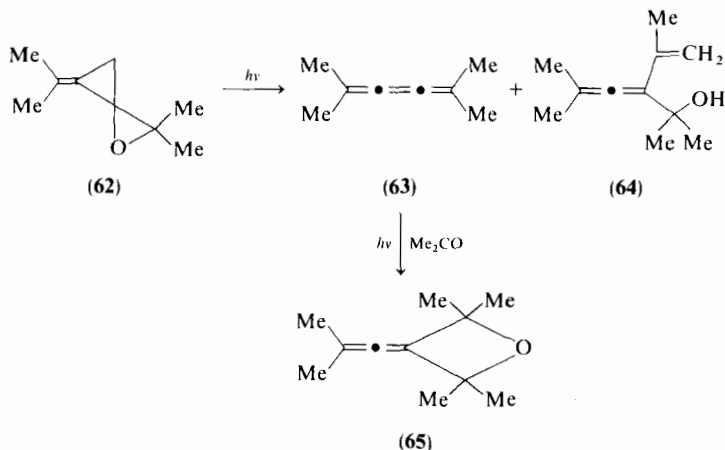


competing 1,2-alkyl migrations, is preferred in the photorearrangement of the steroidal oxiran (**61**), as shown in Scheme 3.⁵² The ketone appears to have



SCHEME 3

little if any role in this transformation, as an analogous rearrangement has been reported in a 4,5-epoxycholest-2-ene.⁵³ An unusual fragmentation, possibly arising via a carbene, is observed on irradiation of the spiro oxiran

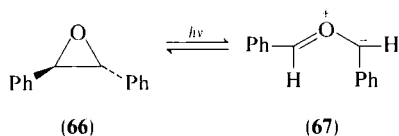


⁵² M. Debono, R. M. Molloy, D. Bauer, T. Iizuka, K. Schaffner, and O. Jeger, *J. Am. Chem. Soc.* **92**, 420 (1970); D. Bauer, T. Iizuka, K. Schaffner, and O. Jeger, *Helv. Chim. Acta* **55**, 852 (1972).

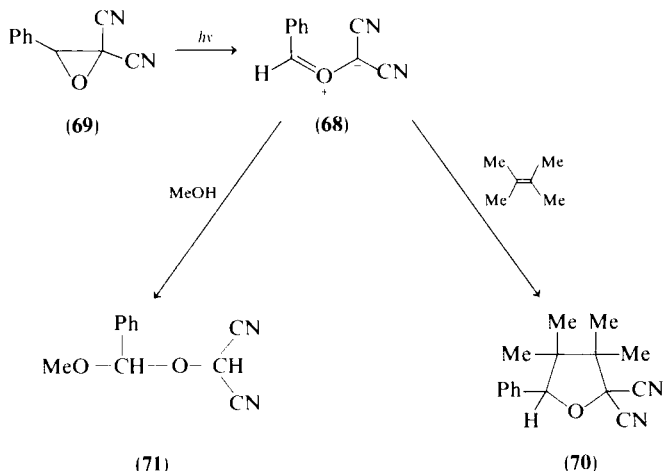
⁵³ J. M. Coxon and G. S. C. Hii, *Aust. J. Chem.* **29**, 1143 (1976).

(62) to give the cumulene (63) and acetone⁵⁴; the allene (64) and the oxetan (65) are also formed, the latter by photoaddition of acetone to the cumulene.

In addition to the photoreactions described above, other transformations have been observed in aryloxirans. 2,3-Diaryloxirans on irradiation undergo reversible carbon-carbon bond cleavage to give carbonyl ylides; *trans*-2,3-diphenyloxiran (66), for example, is converted in this way to the ylide (67). Ring opening is reported to occur from both the singlet and the triplet state,⁵⁵ and in the case of certain cyanodiphenyloxirans, the process has



been shown to proceed in a disrotatory manner.⁵⁶ Carbonyl ylides generated in this way have been trapped chemically and have been detected in low temperature matrices where they exhibit photochromism.⁵⁷ Thus, carbonyl ylide 68, obtained by irradiation of the oxiran (69) in benzene, is converted to adducts 70 and 71 on reaction with 2,3-dimethylbut-2-ene and methanol, respectively.⁵⁸ Carbonyl ylides are also believed to be intermediates in the *cis*-*trans* photoisomerization of several α -cyano- β -arylglycidates,⁵⁹ and the



⁵⁴ J. K. Crandall and D. R. Paulson, *Tetrahedron Lett.*, 2751 (1969).

⁵⁵ G. A. Lee, *J. Org. Chem.* **41**, 2656 (1976).

⁵⁶ V. Markowski and R. Huisgen, *Tetrahedron Lett.*, 4643 (1976).

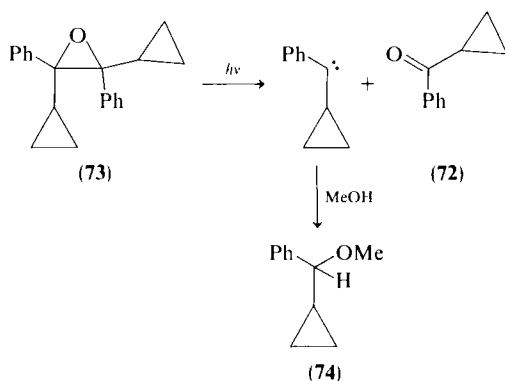
⁵⁷ T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Am. Chem. Soc.* **92**, 1402 (1970); D. R. Arnold and I. A. Karnischky, *ibid.*, 1404.

⁵⁸ I. J. Lev, K. Ishikawa, and G. W. Griffin, *J. Org. Chem.* **41**, 2654 (1976).

⁵⁹ K. Ishikawa, G. W. Griffin, and I. J. Lev, *J. Org. Chem.* **41**, 3747 (1976).

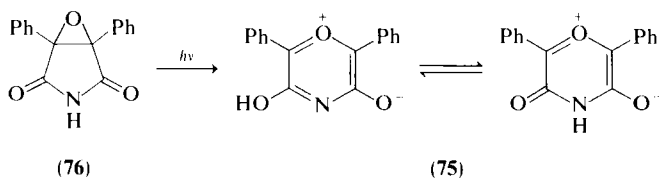
photosensitized (electron-transfer) irradiation both of *cis*- and *trans*-2,3-diphenyloxiran has been shown to result in the formation of carbonyl ylides via oxiran radical-cations.⁶⁰

2,3-Diaryloxirans have long been known to undergo photofragmentation via a $[3 \rightarrow 2 + 1]$ cycloelimination pathway to afford arylcarbenes and carbonyl derivatives.⁶¹ Recent studies suggest that these species arise by further photodecomposition of initially formed carbonyl ylides.⁶² Phenylcyclopropylcarbene, for example, is generated along with phenyl cyclopropyl ketone (**72**) on irradiation of the oxiran (**73**) and undergoes insertion into methanol to give the methyl ether (**74**) in 80% yield.⁶³



Photodecomposition of phosphorus-substituted oxirans provides a useful route to phosphonocarbenes.⁶⁴

Evidence for carbonyl ylide formation has also been reported in bridged diphenyloxirans,⁶⁵ and a particularly stable, highly colored ylide (**75**) is generated on irradiation of the fused oxiran (**76**), both in rigid matrices at



⁶⁰ A. Albini and D. R. Arnold, *Can. J. Chem.* **56**, 2985 (1978).

⁶¹ G. W. Griffin, *Angew. Chem., Int. Ed. Engl.* **10**, 537 (1971).

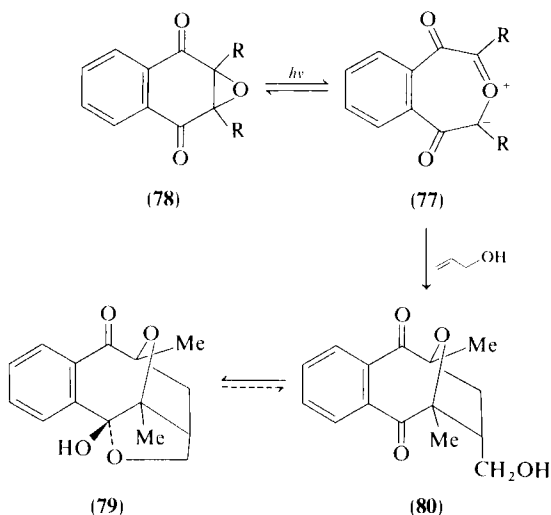
⁶² G. W. Griffin, K. Ishikawa, and I. J. Lev, *J. Am. Chem. Soc.* **98**, 5697 (1976).

⁶³ P. C. Petrellis, G. W. Griffin, M. E. Hendrick, and M. Jones, *J. C. S. Chem. Commun.*, 1002 (1972).

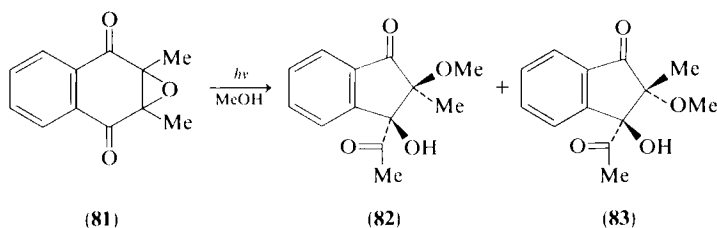
⁶⁴ C. E. Griffin, E. Kraas, H. Terasawa, G. W. Griffin, and D. C. Lankin, *J. Heterocycl. Chem.* **15**, 523 (1978).

⁶⁵ K. Nishiyama, K. Ishikawa, I. Sarkar, D. C. Lankin, and G. W. Griffin, *Heterocycles* **6**, 1337 (1977).

77 K and in the solid state.⁶⁶ The cyclic carbonyl ylide (**77**: R = Ph), obtained by irradiation of 2,3-diphenylnaphthoquinone 2,3-epoxide (**78**: R = Ph), has been trapped with suitable dipolarophiles.⁶⁷ The carbonyl ylide (**77**: R = Me), derived from the 2,3-dimethyloxiran (**78**: R = Me) by irradiation in benzene, adds to allyl alcohol to give the hemiketal (**79**) by way of adduct **80**.⁶⁸ Other 2,3-dialkylnaphthoquinone 2,3-epoxides undergo similar photochemically induced carbon-carbon bond cleavages to give dipolar or biradical species that have been trapped in turn with alkenes⁶⁹ and ketones⁷⁰



and as dimers.⁷¹ The major products of irradiation of the oxiran (**81**) in methanol are ring-contracted adducts **82** and **83**, formed by nucleophilic attack of methanol on an intermediate carbonyl ylide.⁷² Surprisingly, a



⁶⁶ G. W. Griffin, K. Nishiyama, and K. Ishikawa, *J. Org. Chem.* **42**, 180 (1977).

⁶⁷ H. Kato, H. Tezuka, K. Yamaguchi, K. Nowada, and Y. Nakamura, *J. C. S. Perkin I*, 1029 (1978).

⁶⁸ K. Maruyama, A. Osuka, and H. Suzuki, *Chem. Lett.*, 919 (1980).

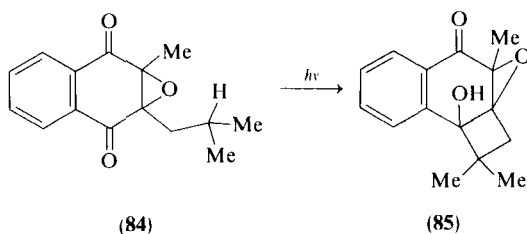
⁶⁹ S. Arakawa, *J. Org. Chem.* **42**, 3800 (1977).

⁷⁰ K. Maruyama and A. Osuka, *Chem. Lett.*, 77 (1979).

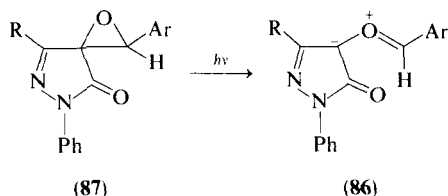
⁷¹ K. Maruyama and A. Osuka, *J. Org. Chem.* **45**, 1898 (1980).

⁷² A. Osuka, H. Suzuki, and K. Maruyama, *Chem. Lett.*, 201 (1981).

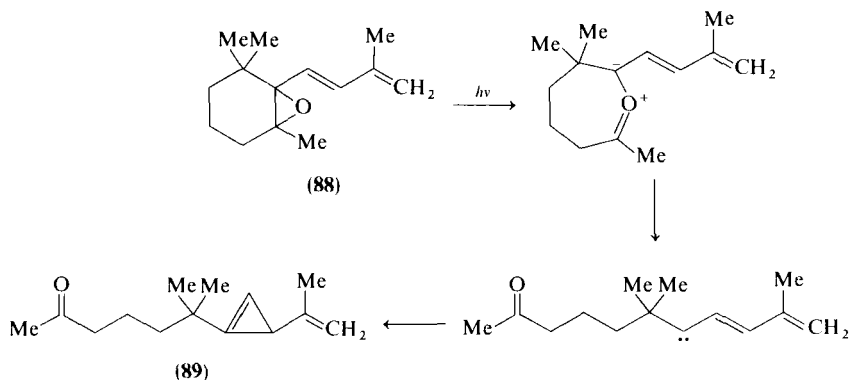
Type II process is preferred on irradiation of epoxynaphthoquinone (**84**) to give a cyclobutanol (**85**).⁷³ Spectroscopic evidence has been described



for the formation of pyrazolinone carbonyl ylides (**86**) on irradiation of spiro oxirans (**87**).⁷⁴



A carbonyl ylide is undoubtedly implicated in the singlet-derived photo-rearrangement of the epoxidiene (**88**) to the cyclopropene (**89**)⁷⁵; a proposed pathway is outlined in Scheme 4. Carbon-oxygen bond homolysis is preferred, however, on triplet-sensitized irradiation, leading to the formation



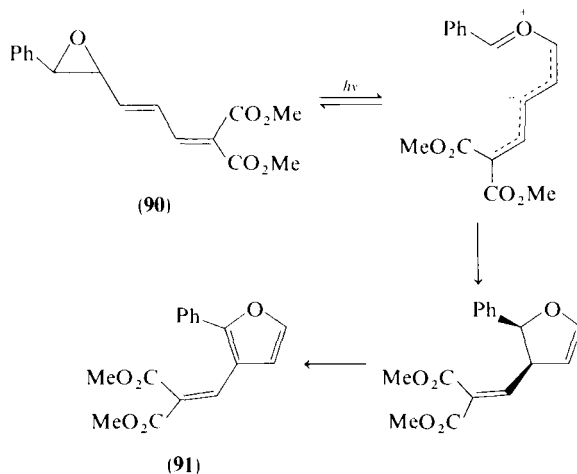
SCHEME 4

⁷³ K. Maruyama, A. Osuka, and H. Suzuki, *J. C. S. Chem. Commun.*, 323 (1980).

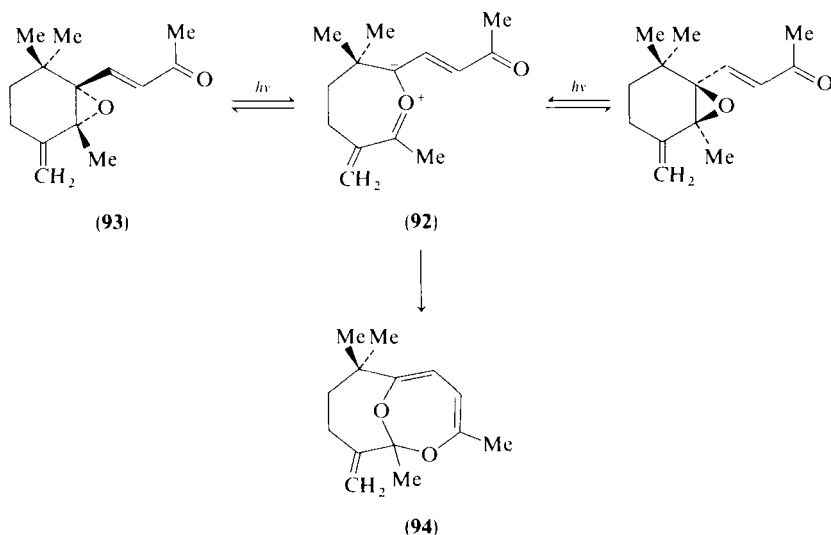
⁷⁴ S. N. Ege, E. J. Gess, A. Thomas, P. Umrigar, G. W. Griffin, P. K. Das, A. M. Trozzolo, and T. M. Leslie, *J. C. S. Chem. Commun.*, 1263 (1980).

⁷⁵ A. P. Alder, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **61**, 2681 (1978).

of alternative products. Analogous behavior has been observed in other 5,6-epoxydienes,⁷⁶ including the butadiene (90), which on irradiation is converted to the furan (91).⁷⁷ Systematic and detailed studies of the photo-



reactions of γ,δ -epoxyenones have been described. An intermediate ylide (92) has been proposed, for example, to account for the photoracemization of the oxiran (93); the existence of this species is supported by the isolation

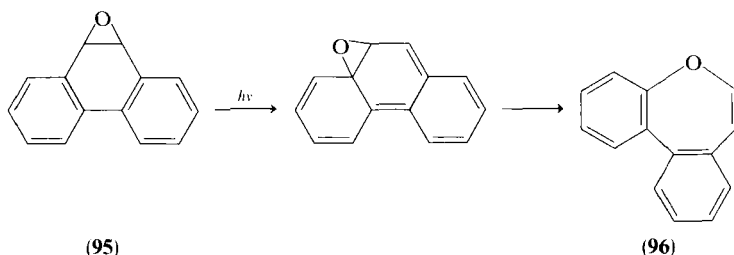


⁷⁶ A. P. Alder, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **64**, 198 (1981).

⁷⁷ W. Eberbach and U. Trostmann, *Tetrahedron Lett.*, 3569 (1977).

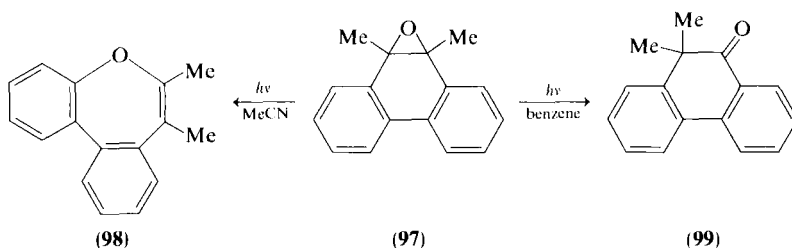
of the bicyclic photoproduct (94).⁷⁸ The formation of a wide variety of products arising by this pathway and by competing carbon–oxygen bond homolysis has been reported in related oxiranes,⁷⁹ in α,β -unsaturated γ,δ -epoxy esters,⁸⁰ in 5,6-epoxy-5-isopropyl-6-methylhept-3-yn-2-one,⁸¹ and in γ,δ -epoxyeucarvone.⁸²

A different pathway is followed on irradiation of “K-region arene oxides” such as 9,10-epoxy-9,10-dihydrophenanthrene (95); the major photoproduct is 2,3:4,5-dibenzoxepin (96), which is believed to arise by a concerted “oxygen-walk” process, as shown in Scheme 5.⁸³ 9-Phenanthrol was also obtained



SCHEME 5

and is formed via the keto tautomer, which has been observed spectroscopically at 77 K.⁸⁴ In this connection, it is interesting to note that, whereas irradiation of the 9,10-dimethyl derivative (97) in acetonitrile again affords



⁷⁸ B. Frei, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **62**, 1668 (1979).

⁷⁹ See, for example, H. Eichenberger, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **59**, 1253 (1976); B. Frei, H. Eichenberger, B. von Wartburg, H. R. Wolf, and O. Jeger, *ibid.* **60**, 2968 (1977); K. Murato, H. R. Wolf, and O. Jeger, *ibid.* **63**, 2212 (1980).

⁸⁰ A. P. Alder, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **63**, 1833 (1980).

⁸¹ H. Eichenberger, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **60**, 743 (1977).

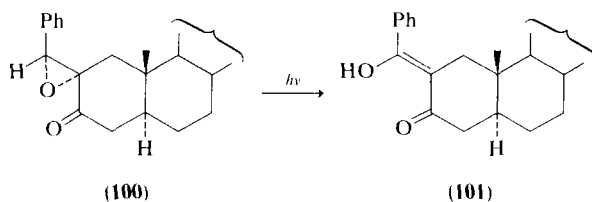
⁸² K. Tsutsumi and H. R. Wolf, *Helv. Chim. Acta* **63**, 2370 (1980).

⁸³ N. E. Brightwell and G. W. Griffin, *J. C. S. Chem. Commun.*, 37 (1973).

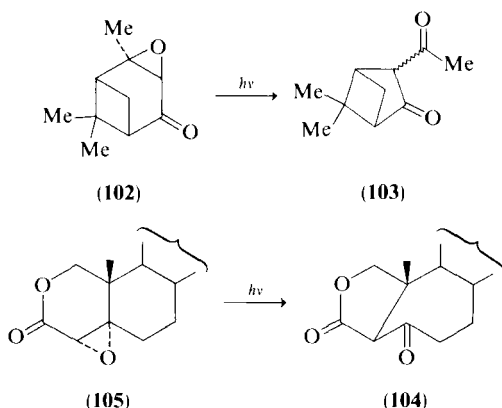
⁸⁴ D. M. Jerina, B. Witcop, C. L. McIntosh, and O. L. Chapman, *J. Am. Chem. Soc.* **96**, 5578 (1974).

the oxepin (**98**), the major photoproduct in benzene solution is 10,10-dimethylphenanthren-9-one (**99**).⁸⁵ Evidence that these products are, respectively, singlet- and triplet-derived has been described.⁸⁶

The photorearrangement of α,β -epoxy ketones has been the subject of further detailed investigations. The major products are 1,3-diketones, although photoepimerization is also observed in chiral oxirans. These transformations have been shown to involve initial carbon-oxygen bond homolysis, followed by 1,2-hydrogen or alkyl migration, as shown for example, for the steroidal oxiran (**100**), which is converted on irradiation to the enol (**101**).⁸⁷ Numerous examples involving cycloalkane ring contraction



have been reported; these include the photorearrangement of (–)-*trans*-verbenone oxide (**102**) to the diketone (**103**)⁸⁸ and the formation of a stable β -oxolactone (**104**) from the oxiran (**105**).⁸⁹ Analogous processes have been



⁸⁵ K. Ishikawa, H. C. Charles, and G. W. Griffin, *Tetrahedron Lett.*, 427 (1977).

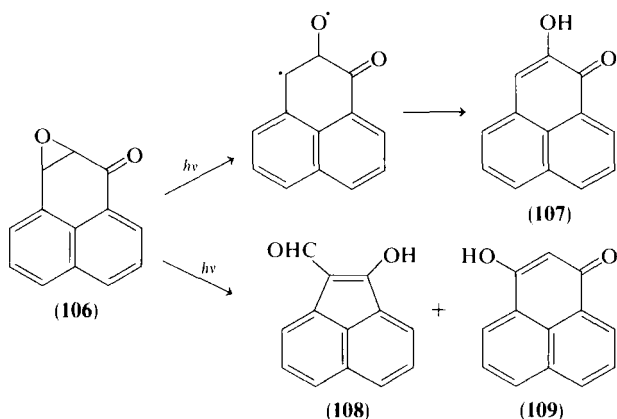
⁸⁶ M. Itoh, K. Murata, K. Tokumura, K. Shudo, N. Miyata, and T. Okamoto, *Tetrahedron* **35**, 1059 (1979).

⁸⁷ J. Muzart and J.-P. Pete, *Tetrahedron* **34**, 1179 (1978).

⁸⁸ T. Gibson, *J. Org. Chem.* **39**, 845 (1974).

⁸⁹ M. J. Caus, A. Cánovas, and J.-J. Bonet, *Helv. Chim. Acta* **63**, 473 (1980).

observed in spiro compounds,⁹⁰ and both carbon–oxygen and carbon–carbon bond cleavage have been shown to occur in aryl-substituted α,β -epoxy ketones.⁹¹ It is surprising to note that an alternative carbon–oxygen bond homolysis is preferred in phenalen-1-one oxide (106) leading to the photoproduct (107); enols 108 and 109 arising by a conventional homolysis are also obtained, but in low yield.⁹² Competing Norrish Type II photocyclization to give stereoisomeric cyclobutanols has been observed in certain appropriately substituted α,β -epoxy ketones.⁹³



The biradical formed on photolysis of 2,3-epoxy-cyclohexane-1,4-dione (110) undergoes further reaction, as shown in Scheme 6, to give the butyrolactone (111); this transformation is expected to be of use in the synthesis of naturally occurring 3-alkylidenephthalides.⁹⁴ Quinone epoxides have been shown to undergo similar photoisomerizations.⁹⁵ The presence of an additional double bond can also influence the course of the photoreaction. An unprecedented rearrangement is observed on $\pi \rightarrow \pi^*$ excitation of α,β -epoxyeucarvone (112) to give the cyclopropane (113)⁹⁶; a pathway involving carbon–carbon bond cleavage and the formation of an intermediate furan

⁹⁰ H.J. Wüthrich, A. Siewinski, K. Schaffner, and O. Jeger, *Helv. Chim. Acta* **56**, 239 (1973); J. R. Williams, G. M. Sarkisian, J. Quigley, A. Hasiuk, and R. V. Vennen, *J. Org. Chem.* **39**, 1028 (1974).

⁹¹ G. A. Lee, *J. Org. Chem.* **43**, 4256 (1978); P. Hallet, J. Muzart, and J.-P. Pete, *Tetrahedron Lett.*, 2723, 2727 (1979).

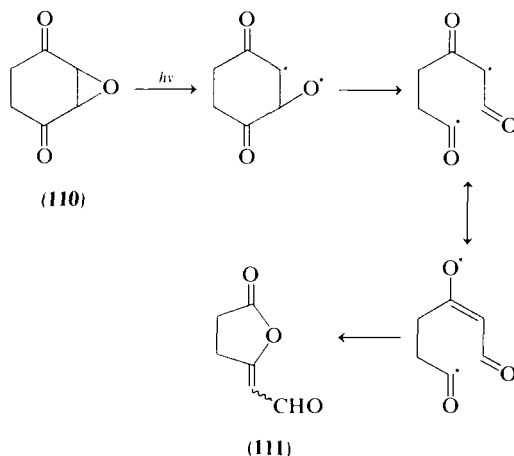
⁹² S. P. Pappas, R. M. Gresham, and M. J. Miller, *J. Am. Chem. Soc.* **92**, 5797 (1970).

⁹³ E. P. Müller and O. Jeger, *Helv. Chim. Acta* **58**, 2173 (1975).

⁹⁴ T. Kitamura, Y. Kawakami, T. Imagawa, and M. Kawanisi, *Tetrahedron* **36**, 1183 (1980).

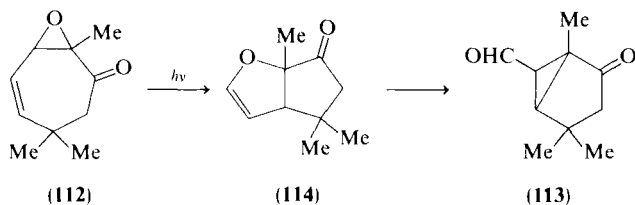
⁹⁵ R. G. F. Giles and I. R. Green, *J. C. S. Chem. Commun.*, 1332 (1972).

⁹⁶ B. Frei and H. R. Wolf, *Helv. Chim. Acta* **59**, 82 (1976).

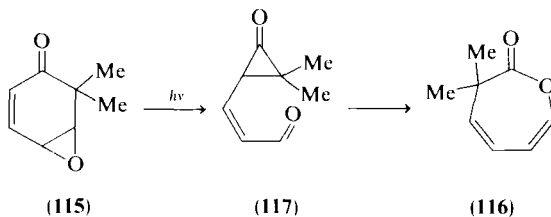


SCHEME 6

(114) has been proposed. A general scheme accounting for the photoisomerization reactions of α,β -unsaturated γ,δ -epoxy ketones has been advanced.⁹⁷



This includes two new pathways in cyclohexa-2,4-dienone 4,5-epoxides, the first involving the photorearrangement of the 6,6-dimethyl derivative (115) to the enol lactone (116) via the cyclopropane (117), and the second providing the first example of α -cleavage in systems of this type. Carbon-oxygen bond homolysis is almost certainly implicated in the photorearrangement of cyclopentadienone epoxide.⁹⁸

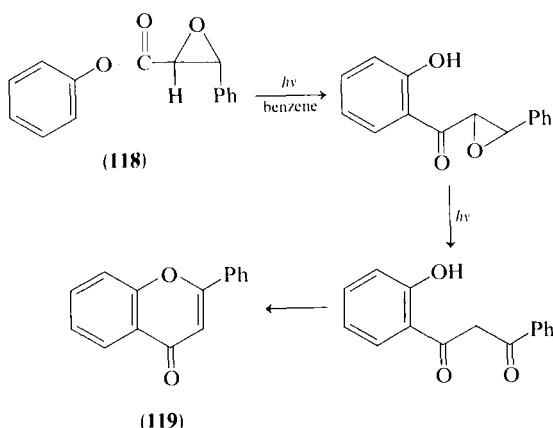


⁹⁷ H. Hart, C. Peng, and E. Shih, *J. Org. Chem.* **42**, 3635 (1977).

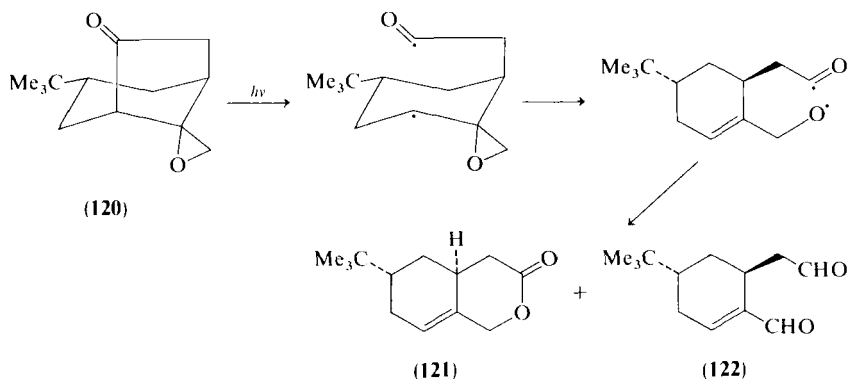
⁹⁸ O. L. Chapman and T. C. Hess, *J. Org. Chem.* **44**, 962 (1979).

Photochemically induced ring cleavage reactions have also been reported in α,β -epoxydiazomethyl ketones⁹⁹ and in α,β -epoxy esters (glycidic esters).¹⁰⁰ Two separate photoreactions are involved, however, in the rearrangement of phenyl epoxycinnamate (**118**) to the flavone (**119**), as shown in Scheme 7.¹⁰¹

A major pathway on irradiation of β,γ -epoxy ketones has been shown to involve α -cleavage. Thus, oxiran **120**, on irradiation in benzene, is converted



SCHEME 7



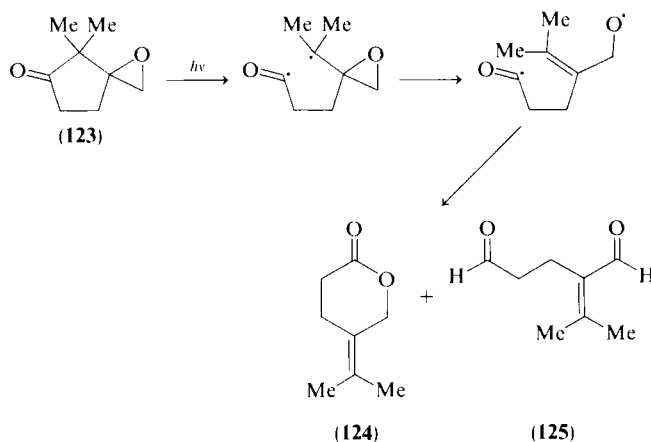
SCHEME 8

⁹⁹ N. F. Woolsey and M. H. Khalil, *J. Org. Chem.* **40**, 3521 (1975); P. M. M. van Haard, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, 803 (1975).

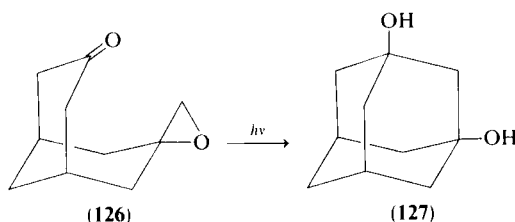
¹⁰⁰ M. Tokuda, V. V. Chung, A. Suzuki, and M. Itoh, *J. Org. Chem.* **40**, 1858 (1975); V. V. Chung, M. Tokuda, A. Suzuki, and M. Itoh, *Bull. Chem. Soc. Jpn.* **49**, 341 (1976).

¹⁰¹ V. T. Ramakrishnan and J. Kagan, *J. Org. Chem.* **35**, 2898 (1970).

to products **121** and **122**, as shown in Scheme 8.¹⁰² Ring opening of the oxiran is not stereospecific, and the same two products are obtained on irradiation of the epimeric oxiran. The spiro oxiran (**123**) is similarly converted, on irradiation in diethyl ether, to the lactone (**124**) and the aldehyde (**125**).¹⁰³



Decarbonylation is observed, however, in substituted 9,10-epoxycholestan-6-ones,¹⁰⁴ and Norrish Type II photocyclization, leading to the formation of cyclobutanols, is preferred in other β,γ -epoxy ketones.¹⁰⁵ A photoreaction of a different type has been observed in the bicyclo[3.3.1]nonane (**126**) and affords the diol (**127**).¹⁰⁶



The photoreactions of thiirans have not been examined in as much detail, although the topic has been the subject of a comprehensive review.¹⁰⁷ Ring cleavage and loss of sulfur is the principal reaction pathway; ethylene, for example, is the major product of direct and benzophenone-sensitized

¹⁰² S. Ayral-Kaloustian and W. C. Agosta, *J. Am. Chem. Soc.* **102**, 314 (1980).

¹⁰³ R. K. Murray and C. A. Andruskiewicz, *J. Org. Chem.* **42**, 3994 (1977).

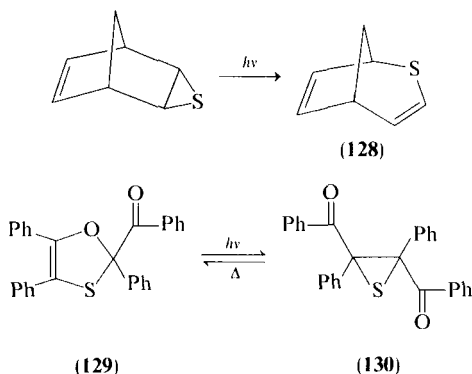
¹⁰⁴ R. J. Chambers and B. A. Marples, *J. C. S. Chem. Commun.*, 1122 (1972).

¹⁰⁵ J. M. Coxon and G. S. C. Hui, *Aust. J. Chem.* **30**, 161, 835 (1977).

¹⁰⁶ T. Mori, K. H. Yang, K. Kimoto, and H. Nozaki, *Tetrahedron Lett.*, 2419 (1970).

¹⁰⁷ A. Padwa, *Int. J. Sulfur Chem., Part B* **7**, 331 (1972).

photodecomposition of thiiran itself.¹⁰⁸ Tetraphenylthiiran is correspondingly converted to 9,10-diphenylphenanthrene.¹⁰⁹ One of the few examples of photochemically induced rearrangement in thiirans is that reported for *exo*-2,3-epithio-5-norbornene, which on irradiation in acetonitrile is converted to the isomer (128).¹¹⁰ The photodecomposition of 1,3-oxathiol (129) to give *cis*- and *trans*-dibenzoylstilbenes has been shown to involve an intermediate thiiran (130),¹¹¹ and photoelimination of sulfur monoxide from 2,3-diphenylthiiran to give diphenylacetylene has been observed on irradiation in benzene.¹¹²



A wavelength-dependent photoreaction has been described in the carbonyl-containing thiiran (131)¹¹³; irradiation at $\lambda = 254$ nm gave the alkene (132), whereas irradiation at $\lambda > 280$ nm gave products 133 and 134 arising by Type I cleavage, followed either by elimination of carbon monoxide or by cyclization to the oxacarbene.

Little has been reported in the period covered by this review on the photo-reactions of oxetans. 2,2,4,4-Tetraphenylloxetan-3-one undergoes decarbonylation on irradiation in benzene to give tetraphenylloxiran and reduction on irradiation in propan-2-ol to give the corresponding oxetan-3-ol.¹¹⁴ The photodecomposition of 1,2-dioxetans is of particular interest; tetramethyl-1,2-dioxetan, for example, undergoes photofragmentation to give electron-

¹⁰⁸ R. Kumar and K. S. Sidhu, *Indian J. Chem.* **11**, 899 (1973).

¹⁰⁹ R. C. Petterson, A. L. Herbert, G. W. Griffin, I. Sarkar, O. P. Strausz, and J. Font, *J. Heterocycl. Chem.* **10**, 879 (1973).

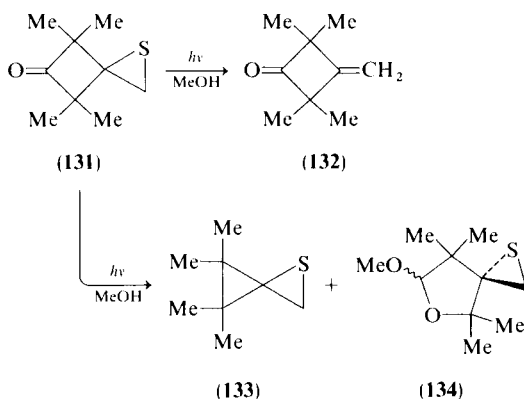
¹¹⁰ T. Fujisawa and T. Kabori, Japan Kokai 74/42677 [*CA* **81**, 135999 (1974)].

¹¹¹ U. Jacobsson, T. Kempe, and T. Norin, *J. Org. Chem.* **39**, 2722 (1974).

¹¹² L. A. Carpino and H.-W. Chen, *J. Am. Chem. Soc.* **101**, 390 (1979).

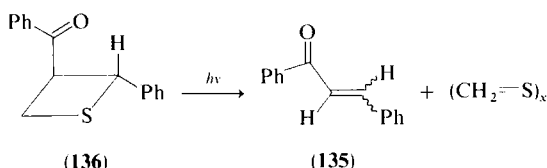
¹¹³ J. G. Pacifici and C. Diebert, *J. Am. Chem. Soc.* **91**, 4595 (1969).

¹¹⁴ J. P. Wasacz, M. M. Joullie, U. Mende, I. Fuss, and G. W. Griffin, *J. Org. Chem.* **41**, 572 (1976).



ically excited acetone, the ratio of singlet to triplet states being wavelength dependent.¹¹⁵ Analogous processes have been observed in 3,4-dimethyl-3,4-di-*n*-butyl-1,2-dioxetan¹¹⁶ and in 3,3:4,4-dibutano-1,2-dioxetan.¹¹⁷ The role of dioxetans in bioluminescence and chemiluminescence has been discussed.¹¹⁸

The products of irradiation of thietan and alkyl-substituted thietans have been explained in terms of an initial carbon-sulfur bond homolysis.¹¹⁹ A similar cleavage has been proposed to account for the formation of *cis*- and *trans*-benzalacetophenone (135) from *trans*-2-phenyl-3-benzoylthietan



(136).¹²⁰ α -Cleavage is observed on irradiation of the dithiolactone (137), leading to the formation in cyclohexane of the dithione (138) and in methanol of the carbene-derived ether (139).¹²¹ Photoelimination of sulfur monoxide from 2,2,4,4-tetraacylthietan 1-oxides has been reported.¹²²

¹¹⁵ N. J. Turro and P. Lechtken, *Tetrahedron Lett.*, 565 (1973); N. J. Turro and W. H. Waddell, *ibid.*, 2069 (1975); P. Lechtken and H.-C. Steinmetzer, *Chem. Ber.* **108**, 3159 (1975).

¹¹⁶ T. R. Darling and C. S. Foote, *J. Am. Chem. Soc.* **96**, 1625 (1974).

¹¹⁷ K. R. Kopecky and J. A. Lopez Sastre, *Can. J. Chem.* **58**, 2089 (1980).

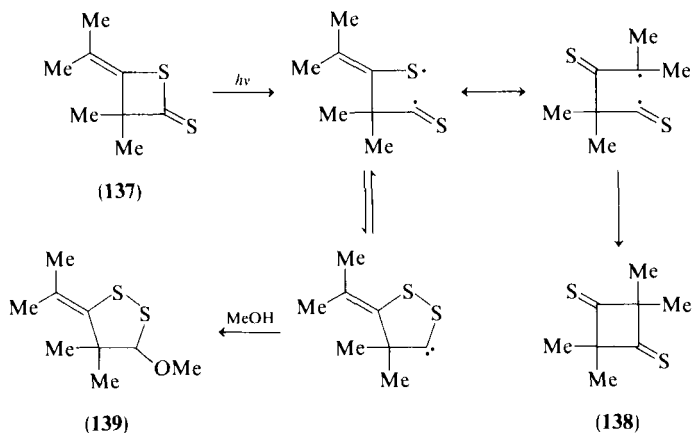
¹¹⁸ J. W. Hastings and T. Wilson, *Photochem. Photobiol.* **23**, 461 (1976).

¹¹⁹ D. R. Dice and R. P. Steer, *Can. J. Chem.* **53**, 1744 (1975).

¹²⁰ A. Padwa and R. Gruber, *J. Org. Chem.* **35**, 1781 (1970).

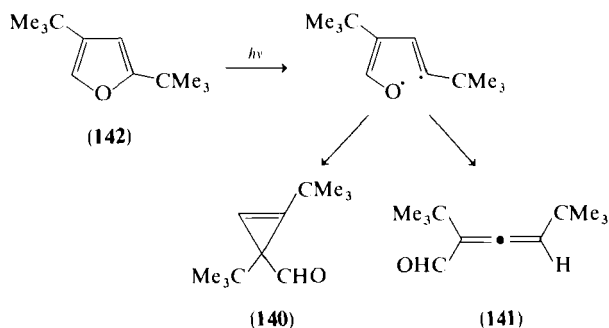
¹²¹ K. Muthuramu and V. Ramamurthy, *J. C. S. Chem. Commun.*, 243 (1980).

¹²² S. Ito and J. Mori, *Bull. Chem. Soc. Jpn.* **51**, 3403 (1978).



2. Five-Membered Heterocycles

One of the major areas of study in the photochemistry of heterocycles is the photorearrangement of five-membered heteroaromatic systems. Various mechanisms have been proposed to account for these transformations.¹²³ A ring contraction–ring expansion pathway, via an intermediate cyclopropene, appears to be involved in the rearrangement of derivatives of furan. The isolation of an intermediate (140) of this type together with an allene (141) has been effected on irradiation of 2,4-di-*tert*-butylfuran (142), as shown in Scheme 9.¹²⁴ Similar transformations have been reported in perfluorotri-

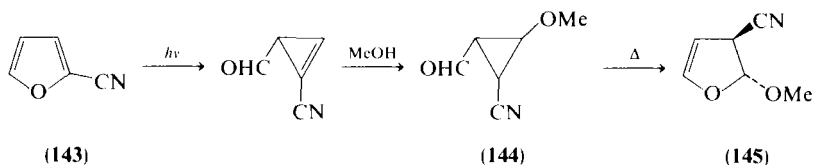


SCHEME 9

¹²³ A. Padwa, "Rearrangements in Ground and Excited States" (P. de Mayo, ed.), Vol. 3, p. 501. Academic Press, New York, 1980.

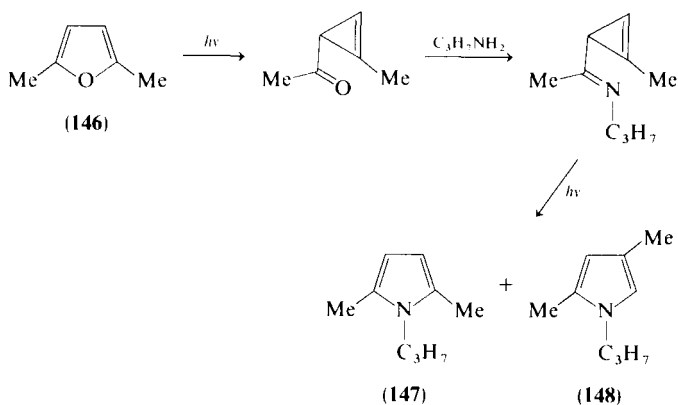
¹²⁴ E. E. van Tamelen and T. H. Whitesides, *J. Am. Chem. Soc.* **93**, 6129 (1971).

and perfluorotetramethylfurans.¹²⁵ Unstable cyclopropene intermediates can be trapped by alcohols or amines; irradiation of 2-cyanofuran (**143**) in methanol affords the ether (**144**), which is further converted to the dihydrofuran (**145**) on heating,¹²⁶ whereas 2,5-dimethylfuran (**146**) on irradiation in



1-aminopropane yields the pyrrole derivatives (**147** and **148**) by the route shown in Scheme 10.¹²⁷ In contrast, irradiation of substituted benzo[*b*]furans in the presence of aliphatic amines results in reduction and the formation of the corresponding dihydrobenzofurans¹²⁸; an electron-transfer process is thought to be involved.

The photoisomerization of thiophen derivatives is much more complex, and both bicyclic and cyclopropene intermediates have been proposed to account for these transformations.¹²⁹ Indeed, tetrakis(trifluoromethyl)-thiophen (**149**) is converted on irradiation to the thermally stable bicycle



SCHEME 10

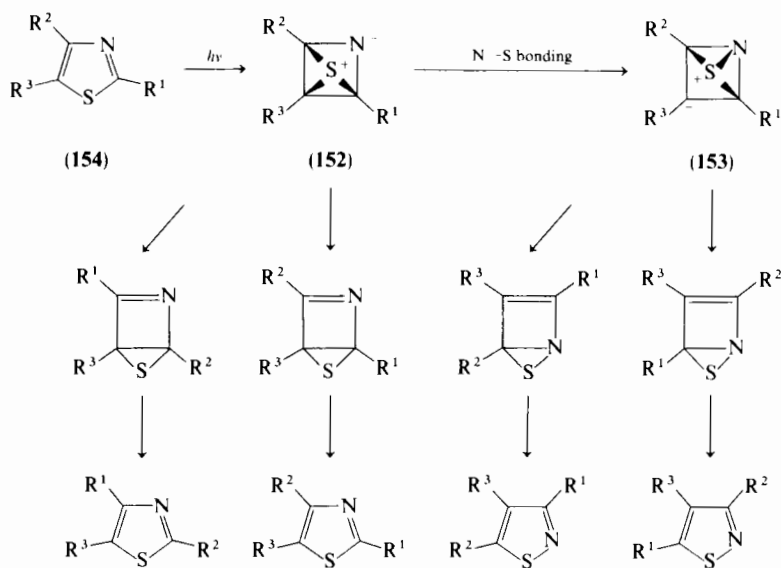
¹²⁵ R. D. Chambers, A. A. Lindley, and H. C. Fielding, *J. Fluorine Chem.* **12**, 337 (1978).

¹²⁶ H. Hiraoka, *Tetrahedron* **29**, 2955 (1973).

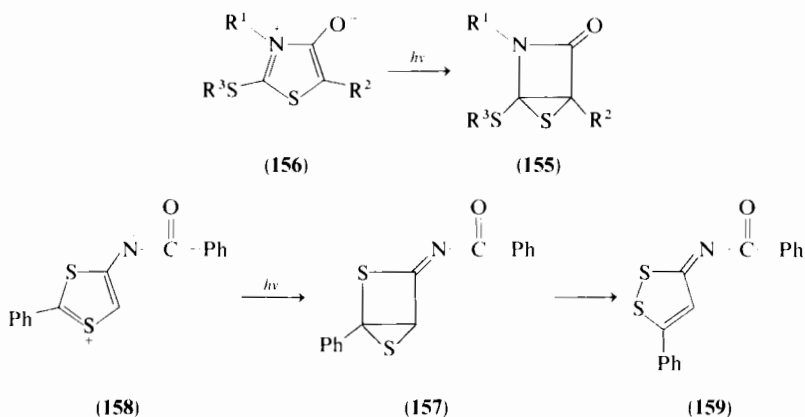
¹²⁷ A. Couture, A. Delevallee, A. Lablache-Combier, and C. Parkanyi, *Tetrahedron* **31**, 785 (1975).

¹²⁸ C. Parkanyi, A. Lablache-Combier, I. Marko, and H. Ofenberg, *J. Org. Chem.* **41**, 151 (1976).

¹²⁹ E. E. van Tamelen and T. Whitesides, *J. Am. Chem. Soc.* **93**, 6129 (1971); H. Wynberg, *Acc. Chem. Res.* **4**, 65 (1971).



SCHEME 12

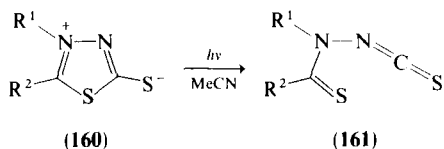


to the imine (159).¹³⁵ In contrast, the related 1,3,4-thiadiazoles (160) undergo photochemically induced ring cleavage to give the thiones (161).¹³⁶ Evidence for an intermediate ketene in the photodecomposition of 4-phenyl 1,3,2-oxathiazol-5-oxide has also been reported.¹³⁷

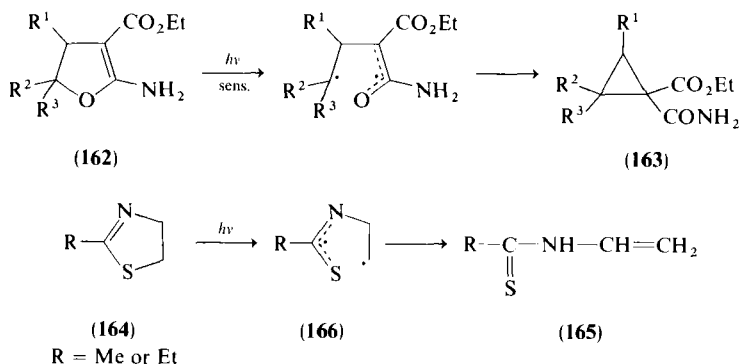
¹³⁵ H. Kato, T. Shiba, H. Yoshida, and S. Fujimori, *J. C. S. Chem. Commun.*, 1591 (1970).

¹³⁶ R. Mukherjee and R. M. Moriarty, *Tetrahedron* **32**, 661 (1976).

¹³⁷ A. Holm, N. Harrit, and N. H. Toubro, *Tetrahedron* **32**, 2559 (1976).



Numerous studies of the photoreactions of dihydrofurans have been described. On irradiation 2,3-dihydrofurans are known to undergo conversion to acylcyclopropanes by a pathway involving initial carbon–oxygen bond homolysis. The β -enamino ester (162), for example, affords the cyclopropane (163) on triplet-sensitized irradiation.¹³⁸ Similar transformations have been observed in 2,2,4-triacyl-2,3-dihydrofurans,¹³⁹ and a synthesis of a cis–trans mixture of chrysanthemum carboxylic acid has been accomplished in this way.¹⁴⁰ The conversion of the 2-thiazolines (164) to the *N*-alkenylthioamides (165) presumably involves an analogous carbon–sulfur bond homolysis, followed by a 1,2-hydrogen shift in the resulting biradical (166).¹⁴¹



Other 2-thiazolines, on irradiation in acetonitrile, undergo fragmentation with the formation of the corresponding nitrile and thiiran.¹⁴² A thiiran (167) was also obtained on irradiation of the 1,3-oxathiole (168),¹⁴³ and the allylic biradical (169) has been proposed as an intermediate in the photochemically induced interconversion of the cyclobutenes (170 and 171).¹⁴⁴ Surprisingly,

¹³⁸ H. Wamhoff, *Chem. Ber.* **105**, 748 (1972).

¹³⁹ K. Ohkata, T. Sakai, Y. Kubo, and T. Hanafusa, *J. Org. Chem.* **32**, 3070 (1978).

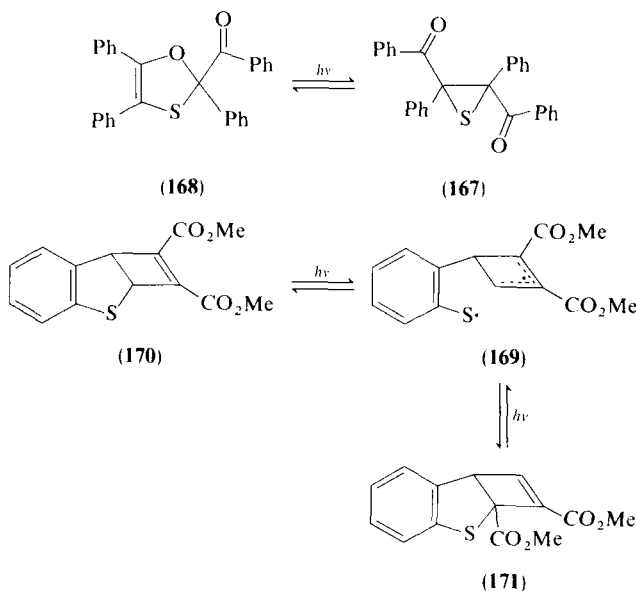
¹⁴⁰ K. Ohkata, T. Isako, and T. Hanafusa, *Chem. Ind. (London)*, 274 (1978).

¹⁴¹ T. Matsuura and Y. Ito, *J. C. S. Chem. Commun.*, 896 (1972).

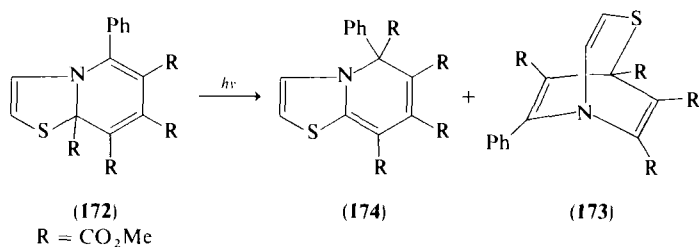
¹⁴² N. Suzuki, K. Kuroyanagi, and Y. Izawa, *Chem. Ind. (London)*, 313 (1977).

¹⁴³ U. Jacobsson, T. Kempe, and T. Norin, *J. Org. Chem.* **39**, 2722 (1974).

¹⁴⁴ S. R. Ditto, P. D. Davis, and D. C. Neckers, *Tetrahedron Lett.*, 521 (1981).



two competing rearrangement pathways have been reported for the pyrido [2,1-*b*]thiazole (172), the first involving a 1,3-sulfur migration to give the isomer (173) and the second, an unusual ester migration to give 174.¹⁴⁵



Direct irradiation of 2,5-dihydrofuran (175) results in the formation of furan, tetrahydrofuran, and the isomeric oxiran (176).¹⁴⁶ Certain 2,5-dihydrothiophen derivatives are similarly converted to the corresponding vinylthiirans,¹⁴⁷ whereas 5,5-diaryl-2,5-dihydrofurans are reported to undergo di- π -methane rearrangement.¹⁴⁸ An unexpected transannular phototransformation has been observed on irradiation of the 1,3-dioxolen-2-one (177)

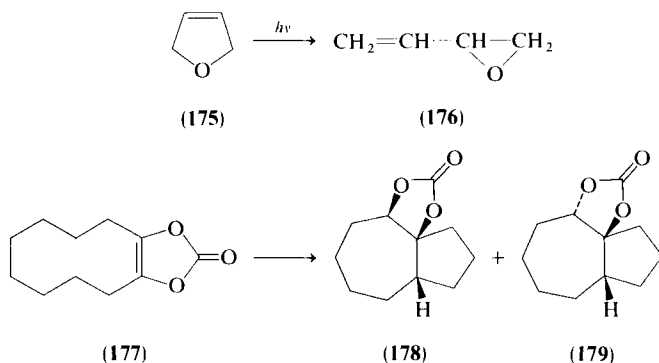
¹⁴⁵ S. Ito, M. Maeda, and M. Kojima, *Heterocycles* **8**, 455 (1977).

¹⁴⁶ S. J. Cristol, G. A. Lee, and A. L. Noreen, *Tetrahedron Lett.*, 4175 (1971).

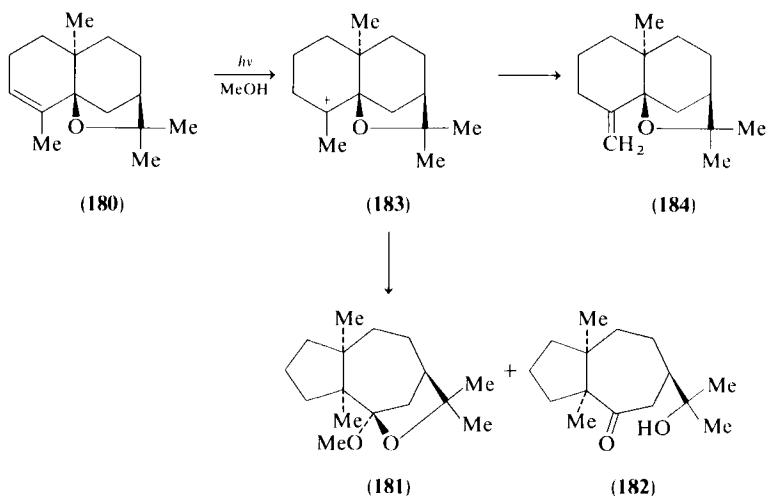
¹⁴⁷ R. M. Kellogg, *J. Am. Chem. Soc.* **93**, 2344 (1971).

¹⁴⁸ A. Padwa and T. Brookhart, *J. Org. Chem.* **44**, 4021 (1979).

to give the carbonates (178 and 179); other 1,3-dioxolen-2-ones undergo photoreduction in propan-2-ol.¹⁴⁹



The photoreactions of saturated five-membered heterocycles are generally characterized by initial carbon-heteroatom bond homolysis. Tetrahydrofurans¹⁵⁰ and 1,3-dioxolans¹⁵¹ behave in this way, and the major photoproducts of 2,2-dimethyl-1,3-dioxolan, for example, are acetone, propyl acetate, ethylene, acetaldehyde, methyl acetate, and oxiran. The vinyltetrahydrofuran (180) is converted on irradiation in methanol to the ketal (181) and the ketone (182) by way of a Wagner-Meerwein shift in the carbocation

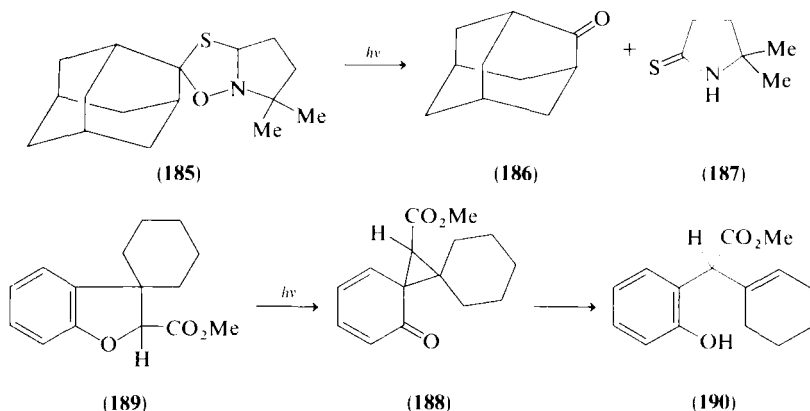


¹⁴⁹ T. Hiyama, S. Fujita, and H. Nozaki, *Bull. Chem. Soc. Jpn.* **44**, 3222 (1971); **45**, 2797 (1972).

¹⁵⁰ N. Kizilkilic, H.-P. Schuchmann, and C. von Sonntag, *Can. J. Chem.* **58**, 2819 (1980).

¹⁵¹ E. Cetinkaya, H.-P. Schuchmann, and C. von Sonntag, *J. C. S. Perkin II*, 985 (1978).

(183)¹⁵²; the isomer (184) was also obtained. Oxygen-oxygen and sulfur-sulfur bond homolyses are reported to occur on irradiation of 1,2-dioxolanes¹⁵³ and 1,2-dithiolanes,¹⁵⁴ respectively, and the 1,4,2-oxathiazolidine (185) undergoes photodecomposition to give adamantanone (186) and the thiolactam (187).¹⁵⁵ An intermediate spiro cyclopropane (188) has been proposed to account for the stereospecific photorearrangement of the dihydrobenzofuran (189) to the phenol (190).¹⁵⁶



The presence of functional groups in the heterocycle frequently determines the nature of the photoreaction observed. The major product of irradiation of 2-methoxyfuran (191) in the gas phase or in solution is the lactone (192).¹⁵⁷ Similarly, 2-nitrofuran (193) undergoes a photoreaction typical of α,β -unsaturated nitro compounds to give the oxime (194) by the pathway shown in Scheme 13.¹⁵⁸ A different process is observed, however, on irradiation of the nitrovinylbenzo[*b*]furan (195) to give the 6-hydroxy-1,2-oxazine (196)¹⁵⁹; this transformation is viewed as proceeding via an electrocyclization pathway (Scheme 14) for which there is a precedent in the known photochromism of nitrostyrenes.

Not surprisingly, the introduction of a carbonyl group into the heterocycle has a profound effect on the photochemistry of the system. The formation of photoproducts arising by a Type I reaction involving 2,3-bond homolysis

¹⁵² A. F. Thomas and M. Ozainne, *Helv. Chim. Acta* **59**, 1243 (1976).

¹⁵³ W. Adam and N. Duran, *Tetrahedron Lett.*, 1357 (1972).

¹⁵⁴ M. Takagi, S. Goto, M. Tazaki, and T. Matsuda, *Bull. Chem. Soc. Jpn.* **53**, 1982 (1980).

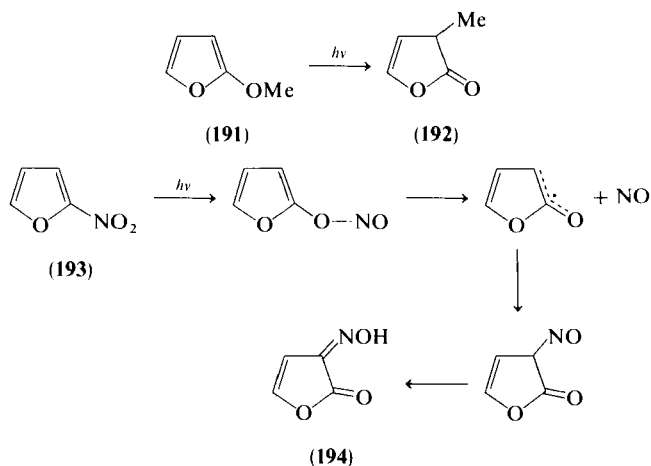
¹⁵⁵ D. S. C. Black and K. G. Watson, *Aust. J. Chem.* **26**, 2491 (1973).

¹⁵⁶ A. G. Schultz, J. J. Napier, and R. Lee, *J. Org. Chem.* **44**, 663 (1979).

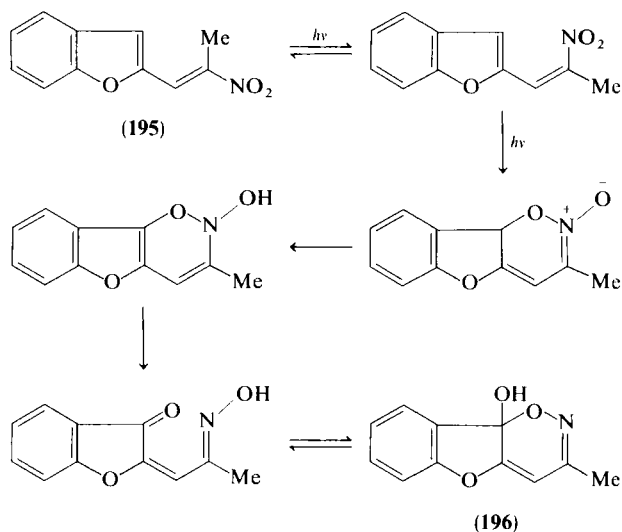
¹⁵⁷ R. Srinivasan and H. Hiraoka, *Tetrahedron Lett.*, 2767 (1969).

¹⁵⁸ R. Hunt and S. T. Reid, *J. C. S. Perkin I*, 2527 (1972).

¹⁵⁹ R. Hunt, S. T. Reid, and K. T. Taylor, *Tetrahedron Lett.*, 2861 (1972).



SCHEME 13



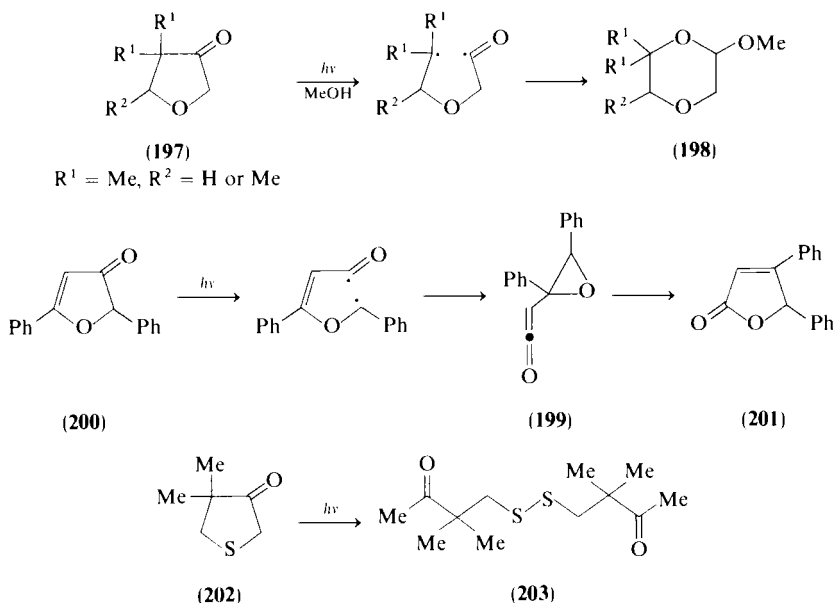
SCHEME 14

has been reported in dihydro-3(2*H*)-furanones¹⁶⁰; in certain highly substituted derivatives (197), an alternative homolysis is preferred, leading to the formation of the cyclic acetals (198).¹⁶¹ 2,3-Bond cleavage followed

¹⁶⁰ G. Hagens, J. P. Wasacz, M. Joullié, and P. Yates, *J. Org. Chem.* **35**, 3682 (1970).

¹⁶¹ P. Yates, A. K. Verma, and J. C. L. Tam, *J. C. S. Chem. Commun.*, 933 (1976).

by ketene formation has been proposed in 2,5-diphenyl-3(2*H*)-furanone (**200**) to account for photorearrangement to the lactone (**201**).¹⁶² A 2-benzyl-2-hydroxybenzo[*b*]furan-3(2*H*)-one has been reported to undergo the photochemical equivalent of a benzilic acid rearrangement.¹⁶³ β -Cleavage is preferred in dihydrothiophen-3(2*H*)-one (**202**) as a result apparently of the greater stability of the thiyl radical; the major product is the disulfide (**203**).¹⁶⁴



In contrast, the thiophenone (**204**) undergoes a stereospecific conrotatory photocyclization via the enol (**205**) to give *cis* fused dihydrobenzo[*b*]thiophen (**206**).¹⁶⁵ Initial nitrogen-sulfur bond homolysis is believed to be responsible for the photoisomerization of isothiazol-3(2*H*)-ones to thiazol-2(3*H*)-ones.¹⁶⁶

The photoreactions of 2(3*H*)- and 2(5*H*)-furanones have also been extensively investigated. 5-Aryl-2(3*H*)-furanones have been shown to undergo initial carbon-oxygen bond homolysis on irradiation,¹⁶⁷ a reaction characteristic of enol lactones. Certain *o*-acetoxyaryl-2(3*H*)-furanones can be converted in this way into chromones. 2(5*H*)-Furanone, on the other

¹⁶² A. Padwa, A. Ku, and E. Sato, *Tetrahedron Lett.*, 2409 (1976).

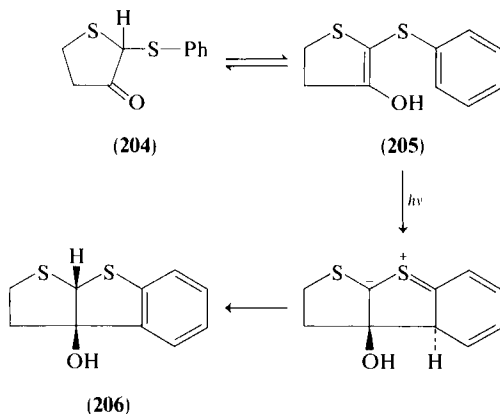
¹⁶³ J. H. van der Westhuizen, D. Ferreira, and D. G. Roux, *J. C. S. Perkin I*, 1517 (1977).

¹⁶⁴ P. Yates and Y. C. Toong, *J. C. S. Chem. Commun.*, 205 (1978).

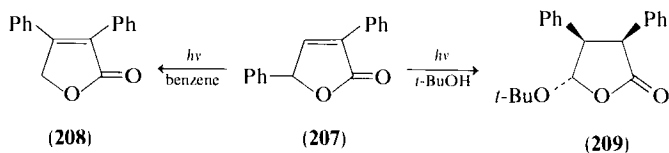
¹⁶⁵ T. Sasaki, K. Hayakawa, and S. Nishida, *Tetrahedron Lett.*, 3903 (1980).

¹⁶⁶ K. Saito and T. Sato, *Bull. Chem. Soc. Jpn.*, **52**, 3601 (1979).

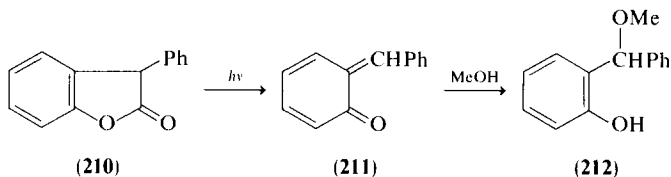
¹⁶⁷ R. Martinez and M. A. Miranda, *Tetrahedron* **37**, 2111 (1981).



hand, does not readily undergo photochemically induced ring opening, and only dimers and solvent adducts are formed.¹⁶⁸ Aryl migration has been reported in 5-aryl-2(5*H*)-furanones, 3,5-diphenyl-2(5*H*)-furanone (207) being converted in this way to 3,4-diphenyl-2(5*H*)-furanone (208) on irradiation in benzene and to the ether (209) on irradiation in *tert*-butanol.¹⁶⁹ A mechanism involving a zwitterionic intermediate has been proposed.



Ring cleavage and decarbonylation has also been observed in benzo[*b*]-furan-2-one.¹⁷⁰ Careful examination of the 3-phenyl derivative has shown that decarbonylation arises by excitation of the keto tautomer (210) and yields the *o*-quinone methide (211)¹⁷¹; this is readily trapped as the ether (212)



¹⁶⁸ B. H. Toder, S. J. Branca, and A. B. Smith, *J. Org. Chem.* **42**, 904 (1977).

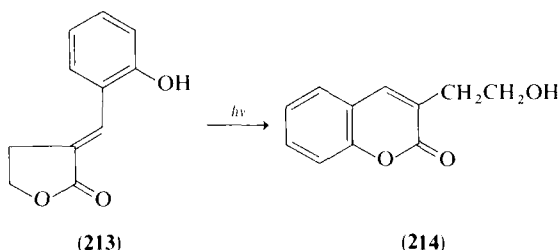
¹⁶⁹ A. Padwa, T. Brookhart, D. Dehm, and G. Wubbels, *J. Am. Chem. Soc.* **100**, 8247 (1978); A. Padwa and D. Dehm, *ibid.* **97**, 4779 (1975).

¹⁷⁰ O. L. Chapman and C. L. McIntosh, *J. C. S. Chem. Commun.*, 383 (1971).

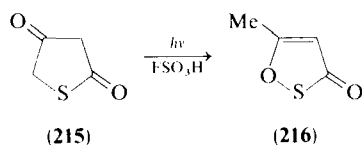
¹⁷¹ A. Padwa, D. Dehm, T. Oine, and G. A. Lee, *J. Am. Chem. Soc.* **97**, 1837 (1975).

(212) with methanol. An analogous ring opening has been reported for benzo[*b*]furan-2,3-dione.¹⁷²

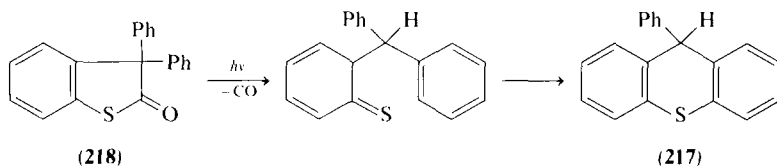
Other γ -lactone containing systems that have been studied include derivatives of 3-oxabicyclo[3.1.0]hexan-2-one¹⁷³ and 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3*H*)-one (213), which on irradiation in methanol undergoes a trans-cis photoisomerization followed by a photochemically induced trans esterification to give the coumarin (214).¹⁷⁴



Analogous transformations are found in the corresponding sulfur-containing systems. Ring cleavage and rearrangement have been observed on irradiation of substituted thiolane-2,4-diones in the presence of base,¹⁷⁵ whereas irradiation of thiolane-2,4-dione itself (215) in fluorosulfonic acid affords the novel 3-oxo-3*H*-1,2-oxathiole (216).¹⁷⁶ The thioxanthene (217)



has been obtained, as shown in Scheme 15, by photodecarbonylation of the dihydrobenzo[*b*]thiophenone (218).¹⁷⁷ 5-Methyl-1,3-benzoxathiol-2-one



SCHEME 15

¹⁷² W. M. Horspool and G. D. Khandelwel, *J. Chem. Soc. C*, 3228 (1971).

¹⁷³ P. C. M. van Noort and H. Cerfontain, *J. C. S. Perkin II*, 757 (1978); 249 (1979).

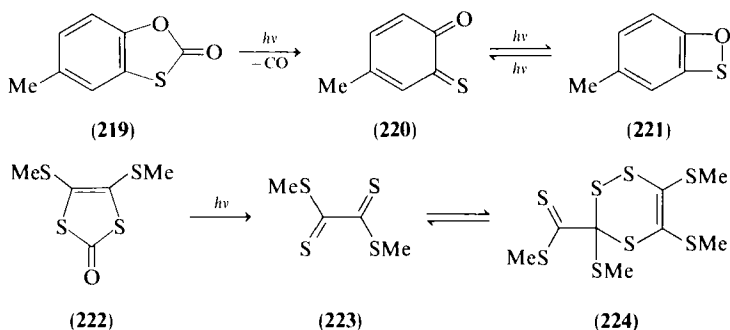
¹⁷⁴ I. R. Bellobono, L. Zanderighi, S. Omarini, B. Marcandalli, and C. Parini, *J. C. S. Perkin II*, 1529 (1975).

¹⁷⁵ K. Saito and T. Sato, *Bull. Chem. Soc. Jpn.*, **52**, 3601 (1979).

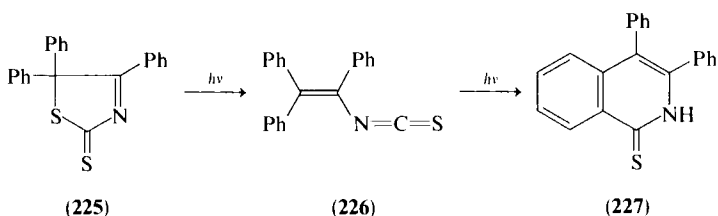
¹⁷⁶ T. Sato, K. Nagumo, K. Saito, T. Ohyama, and R. Nakane, *Chem. Lett.*, 1203 (1979).

¹⁷⁷ J. Nasielski and G. Jacqmin, *Tetrahedron*, **28**, 597 (1972).

(219) is similarly transformed into the transient monothio-*o*-benzoquinone (220) and carbon monoxide¹⁷⁸; at 77 K, this transient is reversibly photoisomerized to benzoxathiet 221. Photodecarbonylation of the 1,3-dithiolan-2-one (222) affords the dithione (223), which in solution has been found to be in equilibrium with the [4 + 2] dimer (224).¹⁷⁹ Details of other studies of the photodecomposition of 1,3-dithiol-2-ones and related systems have been published.¹⁸⁰



Decomposition of a different type is observed on irradiation of the 3-thiazoline-2-thione (225) resulting in loss of sulfur and the formation of the vinyl isothiocyanate (226)¹⁸¹; further irradiation yields the isoquinoline-1-thione (227).



3. Six-Membered Heterocycles

There are few six-membered nonnitrogenous heteroaromatic systems available for study, and systematic examination has been carried out only on the pyrylium cation. It has recently been established that 2,3,5,6-tetramethylpyrylium perchlorate (228), on irradiation in acetonitrile, is converted

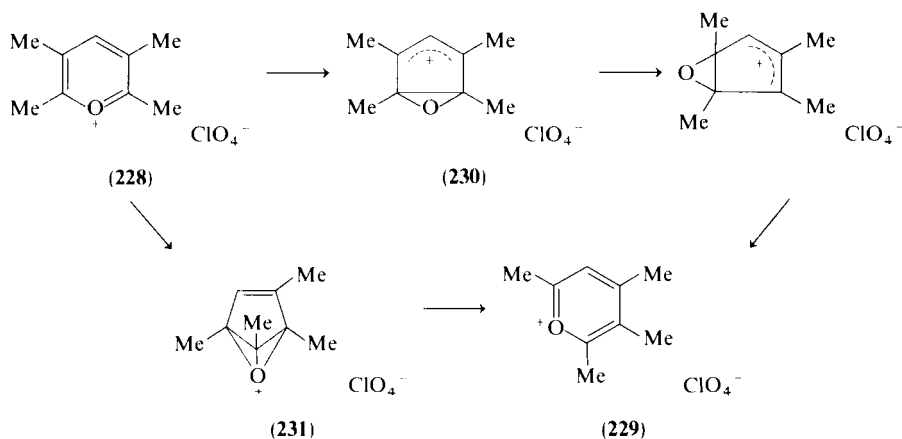
¹⁷⁸ P. de Mayo, A. C. Weedon, and G. S. K. Wong, *J. Org. Chem.* **44**, 1977 (1979).

¹⁷⁹ K. Harte, T. Kissel, J. Quante, and R. Matusch, *Chem. Ber.* **113**, 1898 (1980).

¹⁸⁰ W. Kusters and P. de Mayo, *J. Am. Chem. Soc.* **96**, 3502 (1974); H.-J. Kyi and K. Praefcke, *Tetrahedron Lett.*, 555 (1975); W. Schroth, H. Bahn, and R. Zschernitz, *Z. Chem.* **13**, 424 (1973).

¹⁸¹ A. Q. Hussein, A. Abu-Taha, and J. C. Jochims, *Chem. Ber.* **111**, 3750 (1978).

to the 2,3,4,6-tetramethyl isomer (**229**) via the lowest excited singlet state.¹⁸² Phototransposition occurs only when positions 3 and 5 are substituted by alkyl groups. Two possible mechanistic pathways have been considered, the first involving 2,6-bonding and the formation of cation **230**, and a second in which the oxoniabenzvalene (**231**) has been proposed as an intermediate. An



oxoniabenzvalene intermediate has previously been postulated to account for the photohydration of 2,4,6-trialkylpyrylium cations.¹⁸³ Phototransposition reactions have also been discovered in 4-hydroxypyrylium cations and appear to involve 2,6-bridging leading to the hydroxyoxabicyclohexenyl cation.¹⁸⁴ The formation of 2-hydroxypyrylium salts can normally be rationalized in this way, but in the case of 2,6-di-*tert*-butyl-4-hydroxypyrylium cation (**232**), which is converted on irradiation in sulfuric acid to 4,6-di-*tert*-butyl-2-hydroxypyrylium cation (**233**), a different pathway via "Dewar-type" intermediates has been proposed and is outlined in Scheme 16.¹⁸⁵ Ring contraction is preferred, however, on irradiation of 4-hydroxypyrylium cations in 50% sulfuric acid; thus, 2,3,6-trimethyl-4-hydroxypyrylium cation (**234**) is transformed via a stable cyclopentenone (**235**) into the 2-acetylfuran (**236**),¹⁸⁶ as shown in Scheme 17.

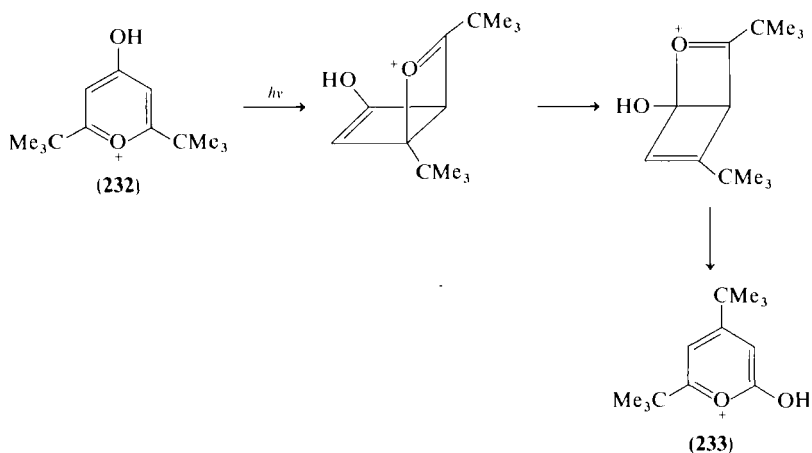
¹⁸² J. A. Barltrop, A. W. Baxter, A. C. Day, and E. Irving, *J. C. S. Chem. Commun.*, 606 (1980).

¹⁸³ J. A. Barltrop, K. Dawes, A. C. Day, and A. J. H. Summers, *J. C. S. Chem. Commun.*, 1240 (1972); J. A. Barltrop, K. Dawes, A. C. Day, S. J. Nuttall, and A. J. H. Summers, *ibid.*, 410 (1973); J. A. Barltrop, K. Dawes, A. C. Day, and A. J. H. Summers, *J. Am. Chem. Soc.* **95**, 2406 (1973).

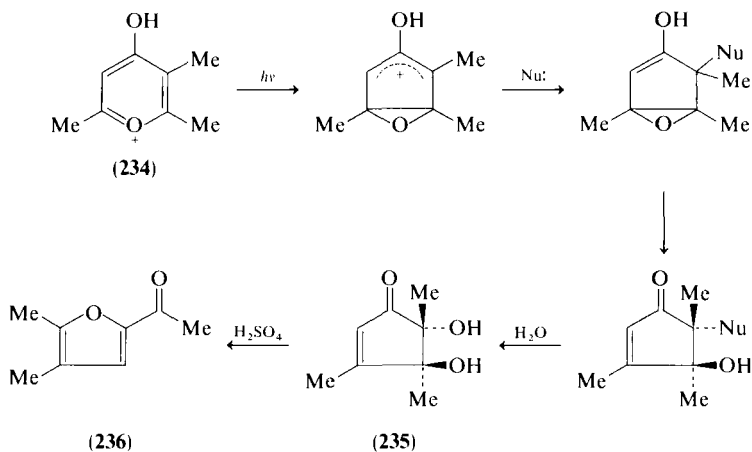
¹⁸⁴ J. W. Pavlik, D. R. Bolin, K. C. Bradford, and W. G. Anderson, *J. Am. Chem. Soc.* **99**, 2816 (1977); J. W. Pavlik and E. L. Clennan, *ibid.* **95**, 1697 (1973); J. A. Barltrop, J. C. Barrett, R. W. Carder, A. C. Day, J. R. Harding, W. E. Long, and C. J. Samuel, **101**, 7510 (1979).

¹⁸⁵ J. W. Pavlik and R. M. Dunn, *Tetrahedron Lett.*, 5071 (1978).

¹⁸⁶ J. W. Pavlik and A. P. Spada, *Tetrahedron Lett.*, 4441 (1979).



SCHEME 16

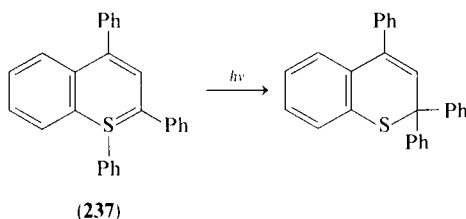


SCHEME 17

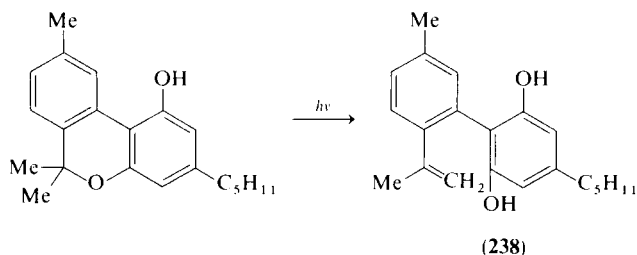
The only comparable sulfur-containing system investigated is that found in thiabenzene¹⁸⁷ and thianaphthalene.¹⁸⁸ In both cases, 1,2-aryl migrations have been observed on irradiation, as shown, for example, in the triphenylthianaphthalene (237). No evidence for any ring transposition reaction in these compounds has been reported.

¹⁸⁷ C. C. Price and H. P. Irelahi, *J. Org. Chem.* **37**, 1718 (1972).

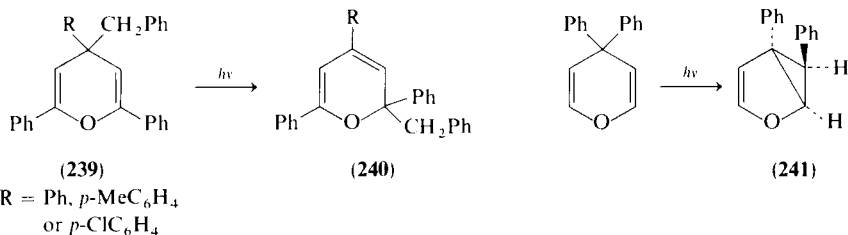
¹⁸⁸ M. Hori, T. Kataoka, and H. Shimizu, *Chem. Pharm. Bull.* **22**, 2485 (1974).



Photochemically induced electrocyclic reactions in *2H*-pyrans have been discussed in preceding sections. Ring cleavage has been reported on irradiation of cannabinol in ethanol to give the alkene **(238)**¹⁸⁹; details of the



mechanism are not clear. Photorearrangement in *4H*-pyrans has also been described. A singlet-derived photochemically induced 1,3-sigmatropic shift of a benzyl group occurs in the *4H*-pyran **(239)** to give the isomeric *2H*-pyran **(240)**.¹⁹⁰ In contrast, 4,4-diphenyl-*4H*-pyran undergoes a di- π -methane rearrangement with 1,2-phenyl migration to give the cyclopropane **(241)**,¹⁹¹ whereas tetraphenyl-1,4-dioxin undergoes photodecomposition via an initial carbon-oxygen bond homolysis.¹⁹²



Oxygen-oxygen bond homolysis is undoubtedly responsible for the conversion of 9,10-diphenylanthracene endoperoxide to the bis-oxiran

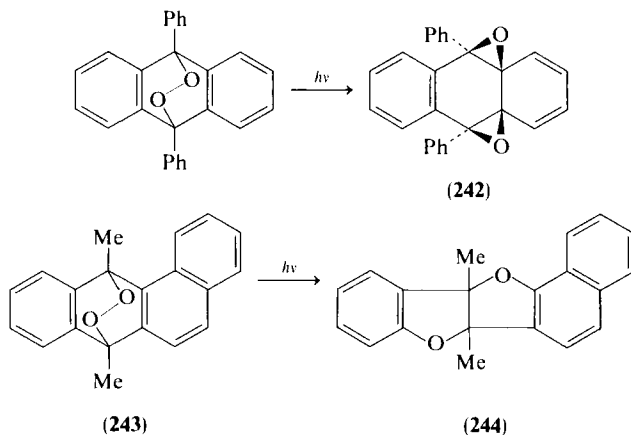
¹⁸⁹ A Bowd, D. A. Swann, and J. H. Turnbull, *J. C. S. Chem. Commun.*, 797 (1975).

¹⁹⁰ F. Fournier, J. Berthelot, N. K. Cuong, and J.-J. Basselier, *Tetrahedron* **35**, 2629 (1979).

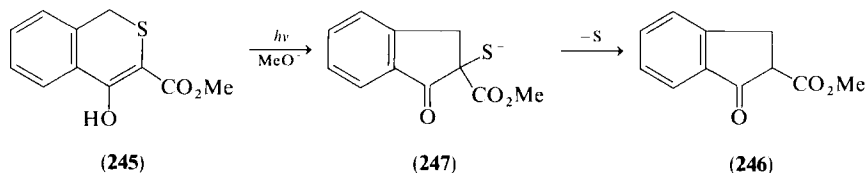
¹⁹¹ D. Gravel, C. Leboeuf, and S. Caron, *Can. J. Chem.* **55**, 2373 (1977).

¹⁹² S. Lahiri, V. Dabral, and M. V. George, *Tetrahedron Lett.*, 2259 (1976).

(242).¹⁹³ Analogous photorearrangements have been reported for other cyclic peroxides,¹⁹⁴ and the conversion of the peroxide (243) to the benzo-furo[3,2-*b*]naphtho[1,2-*d*]furan (244) is believed to involve an intermediate oxiran.¹⁹⁵ Studies of the photodecomposition of 3,4-dihydro-2*H*-pyrans,¹⁹⁶ tetrahydropyran,¹⁹⁷ and 1,4-dioxan¹⁹⁸ have been reported.



Thiopyrans have, in general, been less thoroughly investigated. The isothiochroman-4-one (245) on irradiation in basic methanol is converted to the indanone (246)¹⁹⁹; a pathway involving electrocyclic ring opening and the formation of the intermediate (247) may be implicated. An alternative



¹⁹³ J. Rigaudy, A. Defoin, and J. Baranne-Lafont, *Angew. Chem., Int. Ed. Engl.* **18**, 413 (1979).

¹⁹⁴ J. Rigaudy, C. Brelere, and P. Scribe, *Tetrahedron Lett.*, 687 (1978); J.-P. Hagenbuch and P. Vogel, *ibid.*, 561 (1979); R. Srinivasan, K. H. Brown, J. A. Ors, L. S. White, and W. Adam, *J. Am. Chem. Soc.* **101**, 7424 (1979)

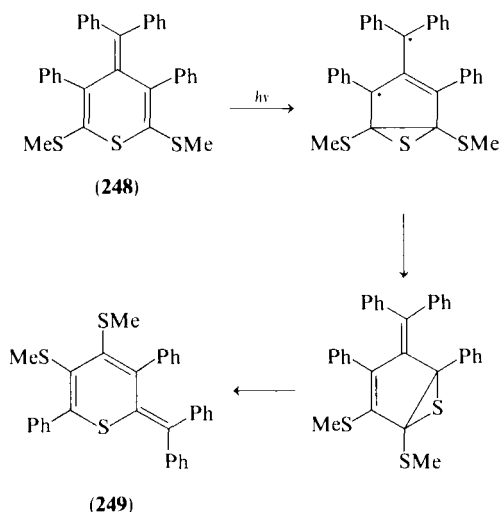
¹⁹⁵ M. K. Logani, W. A. Austin, and R. E. Davies, *Tetrahedron Lett.*, 511 (1978).

¹⁹⁶ R. Srinivasan, *J. Org. Chem.* **35**, 786 (1970).

¹⁹⁷ H. P. Schuchmann, P. Naderwitz, and C. Von Sonntag, *Z. Naturforsch., B:* **33B**, 942 (1978).

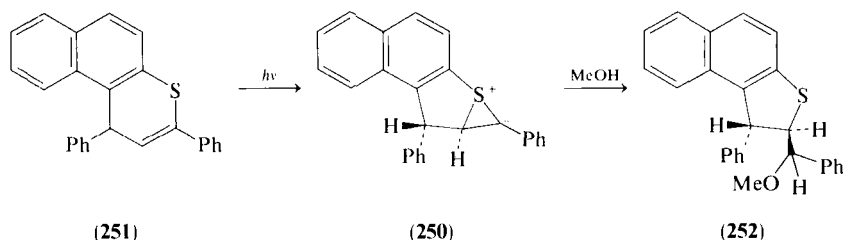
¹⁹⁸ J. J. Houser and B. A. Sibbio, *J. Org. Chem.* **42**, 2145 (1977); J. Kiwi, *J. Photochem.* **7**, 237 (1977); H. P. Schuchmann, H. Bandmann, and C. von Sonntag, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **34B**, 327 (1979).

¹⁹⁹ A. Padwa and A. Au, *J. Am. Chem. Soc.* **98**, 5581 (1976).



SCHEME 18

explanation (Scheme 18) involving 2,6-bonding has been proposed to account for the triplet-derived photorearrangement of the 4-diphenylmethylen-4H-thiopyran (248) to the isomeric 2H-thiopyran (249) in benzene.²⁰⁰ The ylide (250) is a possible intermediate in the conversion of the 4H-thiopyran (251) to dihydrothiophen (252) in methanol.²⁰¹



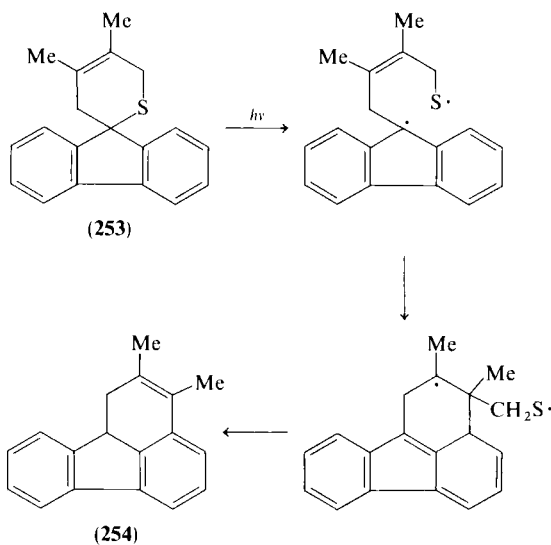
Initial carbon-sulfur bond homolysis is believed to be implicated in the conversion of the spiro dihydrothiopyran (253) to the fluoranthene (254), as shown in Scheme 19.²⁰² Loss of sulfur accompanied by the formation of α,β -unsaturated aldehydes has also been observed on irradiation of the corresponding sulfoxide.²⁰³ An additional competing pathway, leading to

²⁰⁰ N. Ishibe and M. Tamura, *J. Org. Chem.* **41**, 2279 (1976).

²⁰¹ A. G. Schultz and R. M. Schlessinger, *Tetrahedron Lett.*, 4791 (1973).

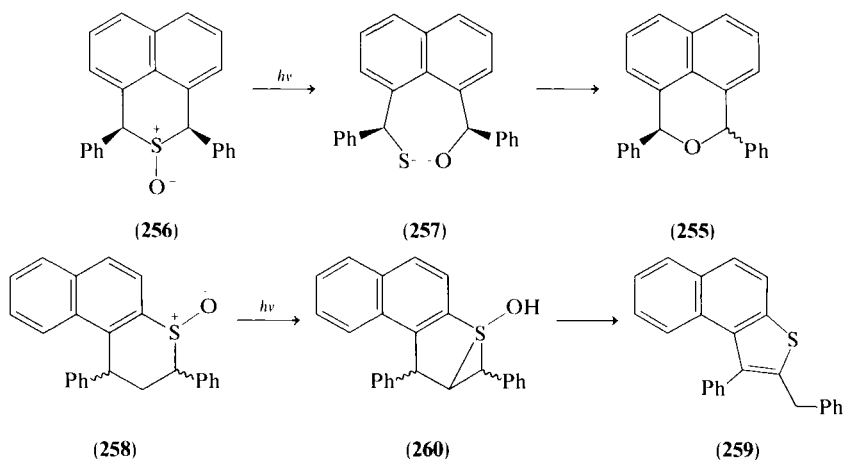
²⁰² K. Praefcke and C. Weichsel, *Justus Liebigs Ann. Chem.*, 1399 (1978).

²⁰³ K. Praefcke and C. Weichsel, *Justus Liebigs Ann. Chem.*, 333 (1980).



SCHEME 19

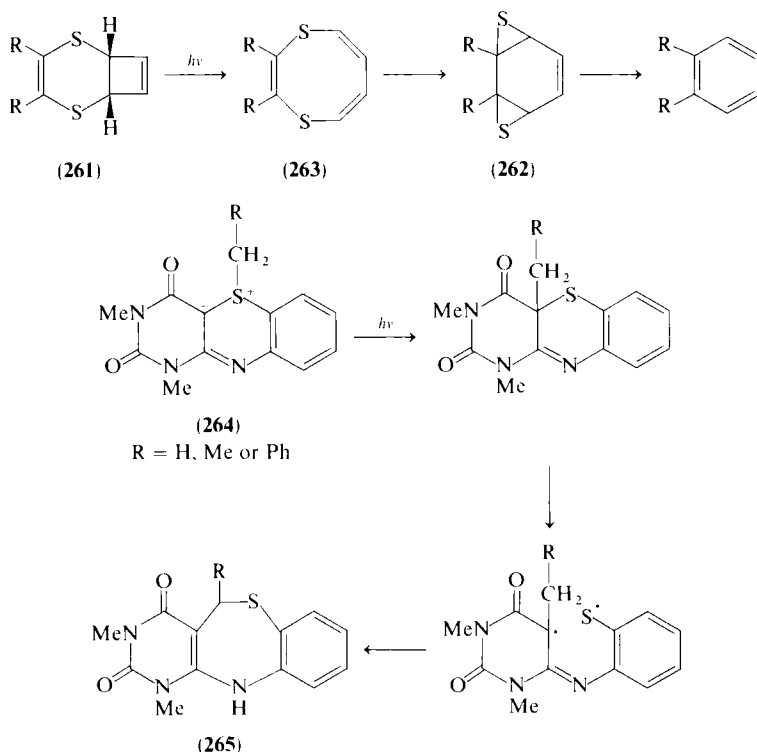
the formation of *cis*- and *trans*-pyrans (255), has been found in the sulfoxide (256); evidence for the intermediacy of the *cis*-sulfenate (257) in this transformation has been reported.²⁰⁴ In contrast, the sulfoxide (258) affords the thiophen (259) on irradiation, possibly via the thiiran (260).²⁰⁵



²⁰⁴ A. G. Schultz and R. H. Schlessinger, *Tetrahedron Lett.*, 3605 (1973).

²⁰⁵ A. G. Schultz and R. H. Schlessinger, *Tetrahedron Lett.*, 4787 (1973).

An example of the photodecomposition of a dithiin to give a stable dithiet, with elimination of ethylene, has been reported.²⁰⁶ A different reaction is preferred in the dithiins (**261**), which on irradiation, are converted to benzene derivatives (**262**) via the 1,4-dithiocins (**263**).²⁰⁷ The cyclic trimer of thioacetophenone on irradiation in cyclohexane yields thioacetophenone.²⁰⁸ An initial carbon-sulfur bond homolysis is also responsible for the conversion, on irradiation in methanol, of a 3-cephem to two thiazoles,²⁰⁹ whereas a 1,2-alkyl migration followed by a further photochemically induced carbon-sulfur bond homolysis has been proposed to account for the photorearrangement of the sulfonium ylides (**264**) to the pyrimido-1,4-benzo[*b*]thiazepines (**265**).²¹⁰ The novel photorearrangement of a 1,3-thiazine to a cyclopropathiazolidine has also been rationalized in terms of an initial carbon-sulfur



²⁰⁶ R. B. Boar, D. W. Hawkins, J. F. McGhie, and D. H. R. Barton, *J. C. S. Perkin I*, 51 (1977).

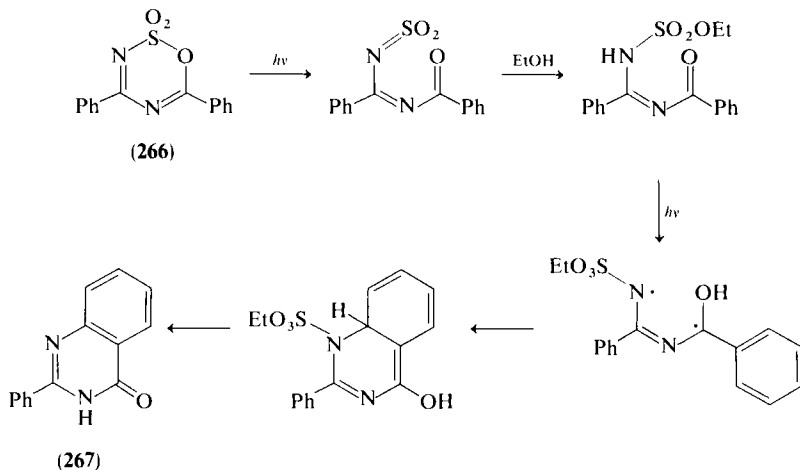
²⁰⁷ D. L. Coffen, Y. C. Poon, and M. L. Lee, *J. Am. Chem. Soc.* **93**, 4627 (1971).

²⁰⁸ T. Nishio, M. Yoshioika, H. Aoyama, and N. Sugiyama, *Bull. Chem. Soc. Jpn.* **46**, 2253 (1973).

²⁰⁹ Y. Maki and M. Sako, *J. Am. Chem. Soc.* **99**, 5091 (1977).

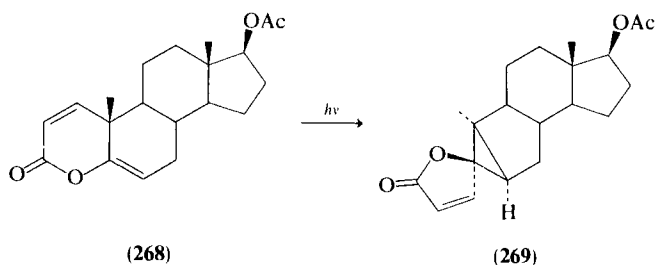
²¹⁰ Y. Maki and T. Hiramutsu, *Chem. Pharm. Bull.* **25**, 292 (1977).

bond homolysis.²¹¹ Ring opening of a different type has been observed on irradiation of the 1,2,3,5-oxathiadiazine (**266**) to give the 4(3*H*)-quinazolinone (**267**)²¹²; details of the proposed mechanism are given in Scheme 20.



SCHEME 20

As in five-membered heterocycles, the introduction of a carbonyl group produces a dramatic effect on the photoreactivity. Pyran-2-ones undergo other electrocyclic processes in addition to those discussed in preceding sections.²¹³ Photorearrangement, however, does not occur in the coumarin nucleus, although a photo-Fries rearrangement of 3-benzoyloxy-6,7-



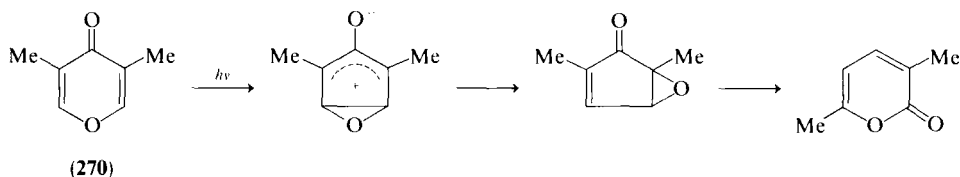
²¹¹ P. B. Hitchcock, R. W. McCabe, D. W. Young, and G. M. Davies, *J. Chem. Soc. Chem. Commun.*, 608 (1981).

²¹² D. F. Eaton and B. E. Smart, *J. Org. Chem.* **44**, 4435 (1979).

²¹³ O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.* **95**, 246 (1973); C. T. Bedford, J. M. Forrester, and T. Money, *Can. J. Chem.* **48**, 2645 (1970).

dimethoxycoumarin to 4-benzoyl-3-hydroxy-6,7-dimethoxycoumarin has been reported.²¹⁴ A di- π -methane rearrangement has been observed in the α,β -unsaturated δ -lactone (**268**) and affords the spiro γ -lactone (**269**)²¹⁵; photorearrangement in other steroidal δ -lactones has been described.²¹⁶

Sufficient evidence has now been obtained to provide an explanation for the photorearrangement of pyran-4-ones to the isomeric pyran-2-ones.²¹⁷ An oxabicyclohexenyl zwitterion and a cyclopentadienone epoxide have been established as intermediates in this rearrangement, and the process is illustrated for 3,5-dimethylpyran-4-one (**270**) in Scheme 21. Related transformations have been observed in 3-hydroxypyran-4-ones²¹⁸ and in the



SCHEME 21

chromones (**271**), which on irradiation are converted to the isocoumarins (**272**)²¹⁹; a stilbene-to-phenanthrene photocyclization occurs on prolonged irradiation to give the pentacyclic ring system (**273**). 3-Hydroxyflavones have been similarly converted to 3-aryl-3-hydroxyindane-1,2-diones.²²⁰ Both ring cleavage and reduction, the latter arising via hydrogen abstraction from the solvent, have been reported on irradiation of flavonones.²²¹ The photochemistry of flavonoids has been reviewed elsewhere.²²²

²¹⁴ V. G. S. Box and Y. A. Jackson, *Heterocycles* **14**, 1265 (1980).

²¹⁵ J. A. Vallet, J. Boix, J.-J. Bonet, M. C. Brioso, C. Miravittles, and J. L. Brioso, *Helv. Chim. Acta* **61**, 1158 (1978).

²¹⁶ V. Ferrer, J. Gómez, and J.-J. Bonet, *Helv. Chim. Acta* **60**, 1357 (1977); A. Cánovas and J.-J. Bonet, *ibid.* **63**, 2390 (1980).

²¹⁷ J. A. Barltrop, A. C. Day, and C. J. Samuel, *J. Am. Chem. Soc.* **101**, 7521 (1979).

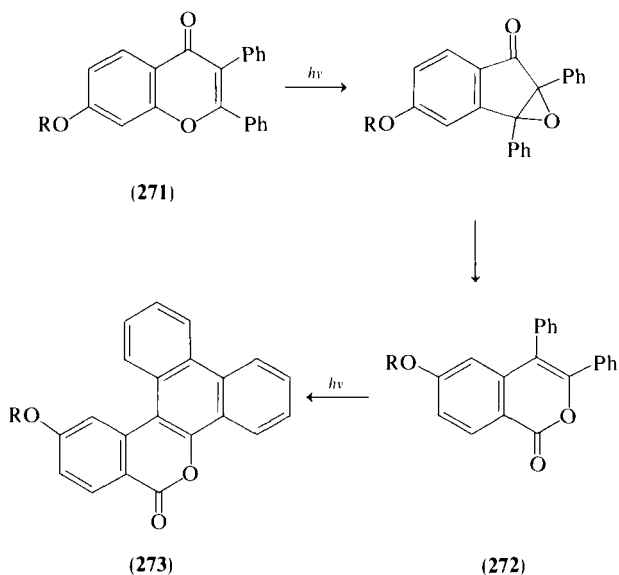
²¹⁸ M. Shiozaki and T. Hiraoka, *Tetrahedron Lett.*, 4655 (1972); D. H. R. Barton and L. A. Hulshof, *J. C. S. Perkin I*, 1103 (1977).

²¹⁹ N. Ishibe and S. Yutaka, *Tetrahedron* **32**, 1331 (1976).

²²⁰ T. Matsuura, T. Takemoto, and R. Nakashima, *Tetrahedron* **29**, 3337 (1973).

²²¹ P. O. L. Mack and J. T. Pinhey, *J. C. S. Chem. Commun.*, 451 (1972); R. Nakashima, K. Okamoto, and T. Matsuura, *Bull. Chem. Soc. Jpn.* **49**, 3355 (1976); R. Matsushima, T. Kishimoto, M. Suzuki, M. Morioka, and H. Mizuno, *ibid.* **53**, 2938 (1980).

²²² A. C. Jain, H. R. Saini, and R. C. Gupta, *J. Sci. Ind. Res.* **37**, 264 (1978).



Two distinct photoreactions have been found in 4-phenylchroman-3-one (274).²²³ The first arises by initial carbon–oxygen bond homolysis and leads, as shown in Scheme 22, to 2-phenylchroman-3-one (275), whereas the second, which is preferred in polar solvents such as methanol, is the result of electrocyclic ring opening of the enol tautomer and yields the *o*-quinoneallide (276). The enol tautomer is also implicated in the photorearrangement of 3-carbomethoxyisochromanone.²²⁴

Other oxygen-containing systems that have been studied include 2,2,6,6-tetramethyltetrahydropyran-3-one,²²⁵ 2-alkoxytetrahydropyran-3-ones,²²⁶ 2-acyl-2,3-dihydro-4*H*-pyrans,²²⁷ cyclic acetals,²²⁸ and a wide variety of carbonyl-containing pyranoside derivatives.²²⁹

²²³ A. Padwa, A. Au, and W. Owens, *J. Org. Chem.* **43**, 303 (1978).

²²⁴ A. Padwa and A. Au, *J. Am. Chem. Soc.* **98**, 5581 (1976).

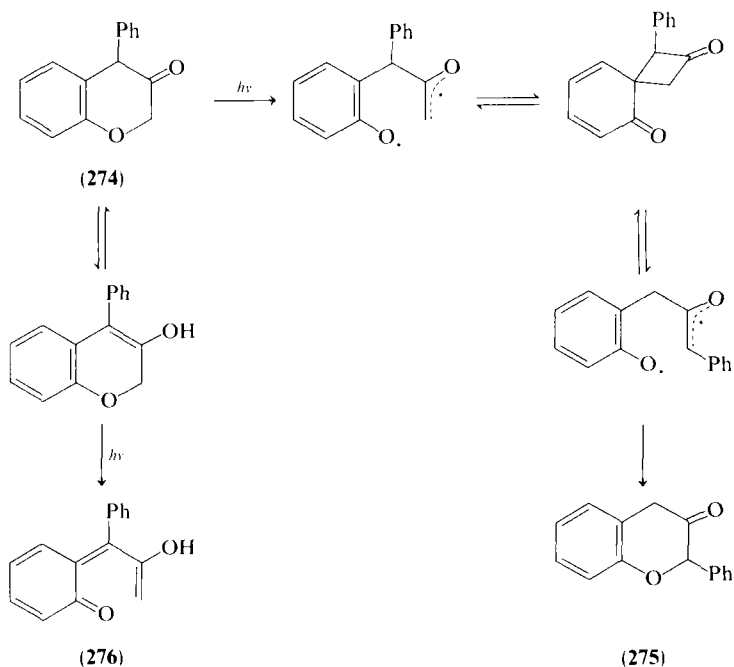
²²⁵ J. P. Wasacz and M. M. Joullie, *Tetrahedron Lett.*, 2501 (1970).

²²⁶ C. Bernasconi, L. Cottier, G. Descotes, M. F. Grenier, and F. Metras, *Nouv. J. Chim.* **2**, 79 (1978); *J. Heterocycl. Chem.* **17**, 45 (1980).

²²⁷ P. Chaquin, J.-P. Morizur, and J. Kossanyi, *J. Am. Chem. Soc.* **99**, 903 (1977); P. Chaquin, B. Furth, and J. Kossanyi, *Recl. Trav. Chim. Pays-Bas* **98**, 346 (1979).

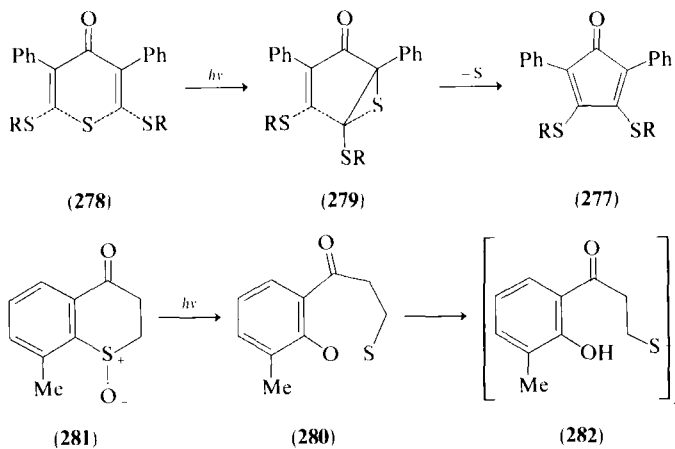
²²⁸ T. Yamagishi, T. Yoshimoto, and K. Minami, *Tetrahedron Lett.*, 2795 (1971); C. Bernasconi, L. Cottier, and G. Descotes, *Bull. Soc. Chim. Fr.*, 101 (1977); B. W. Babcock, D. R. Dimmel, D. P. Graves, and R. D. McKelvey, *J. Org. Chem.* **46**, 736 (1981).

²²⁹ G. Remy, L. Cottier, and G. Descotes, *Tetrahedron Lett.*, 1847 (1979); P. M. Collins, R. Iyer, and A. S. Travis, *J. Chem. Res., Synop.*, 446 (1978), and references quoted therein.



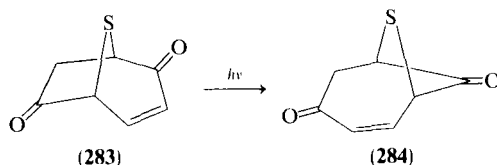
SCHEME 22

Few carbonyl-containing sulfur heterocycles have been studied. Cyclopentadienones (**277**) have been obtained by irradiation of thiopyran-4-ones (**278**), possibly via the thiirans (**279**).²³⁰ A cyclic sulfenate (**280**) has again

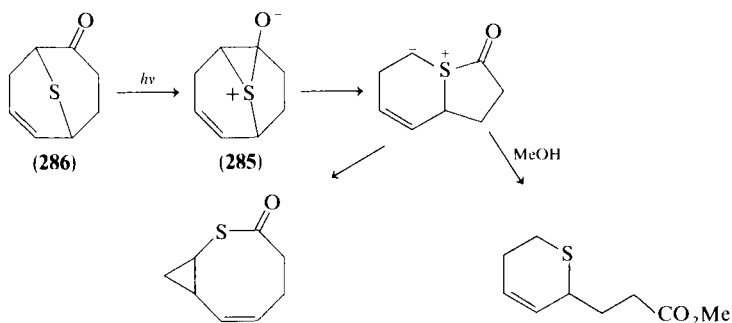


²³⁰ N. Ishibe, M. Odani, and R. Tanuma, *J. C. S. Perkin I*, 1203 (1972).

been proposed to account for the photochemically induced conversion of the sulfoxide (**281**) to the disulfide (**282**)²³¹; the ketone group does not, in this case, appear to have any influence on the reactivity. A 1,3-sigmatropic shift is implicated in the photorearrangement of 8-thiabicyclo[3.2.1]oct-3-en-2-one (**283**) to the thietan-3-one (**284**),²³² whereas there is considerable evidence



for the intermediacy of the zwitterion (**285**) in the photoreactions of 9-thiabicyclo[3.3.1]non-6-en-2-one (**286**)²³³; the products are shown in Scheme 23.



SCHEME 23

4. Seven-Membered and Larger Heterocycles

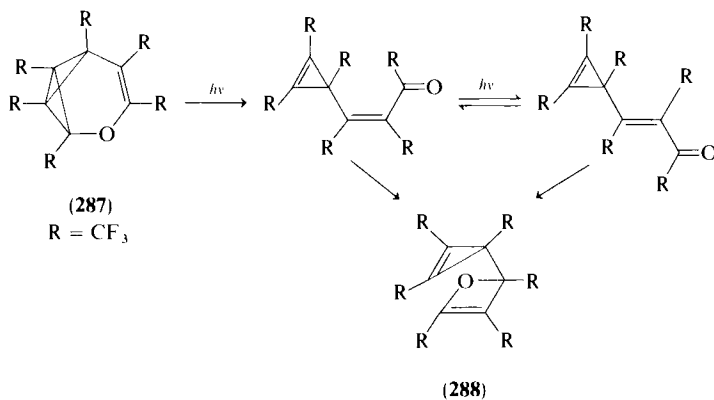
Relatively few examples of photoreactions of seven-membered and larger heterocycles have been reported. The major products of irradiation of liquid oxepin are hex-5-en-1-ol and hexanal²³⁴; photodecomposition of cyclic ethers has, in general, been shown to be largely dependent on ring size. Irradiation of the valence bond isomer (**287**) of hexakis(trifluoromethyl)oxepin gave the unexpectedly stable oxet (**288**) via a mixture of (*Z*)- and

²³¹ I. W. J. Still, P. C. Arora, M. S. Chauhan, M. H. Kwan, and M. T. Thomas, *Can. J. Chem.* **54**, 455 (1976).

²³² H. Tsuruta, M. Ogasawara, and T. Mukai, *Chem. Lett.*, 887 (1974).

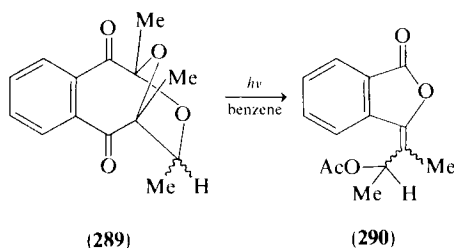
²³³ A. Padwa and A. Battisti, *J. Am. Chem. Soc.* **94**, 521 (1972).

²³⁴ H.-P. Schuchmann and C. von Sonntag, *J. Photochem.* **13**, 347 (1980).



SCHEME 24

(*E*)-1,2,3-tris(trifluoromethyl)-3-[1,2,3-tris(trifluoromethyl)cyclopropenyl]-propenone, as shown in Scheme 24.²³⁵ Initial carbon-oxygen bond homolysis has been proposed to account for photorearrangement in 4,5-dihydrooxepin²³⁶ and in the tetrahydrooxepin ring of mortonin,²³⁷ whereas initial cleavage α to the carbonyl group is thought to be responsible for ring contraction of the phthaloyl derivative (289) to (*Z*)- and (*E*)-alkylidene phthalides (290).²³⁸



7-Phenyl-2(7*H*)-oxepinones (291) undergo triplet-sensitized photorearrangement to the 3-phenyl-2(3*H*)-oxepinones (292).²³⁹ Secondary products 293 and 294 were obtained on further irradiation; the principal products of irradiation in the presence of acid are the 5-styryl-2(5*H*)-furanones (295).²⁴⁰

²³⁵ Y. Kobayashi, Y. Hanzawa, W. Miyashita, T. Kashiwagi, T. Nakano, and I. Kumadaki, *J. Am. Chem. Soc.* **101**, 6445 (1979).

²³⁶ R. D. Cockroft, E. E. Waali, and S. J. Rhoads, *Tetrahedron Lett.*, 3539 (1970).

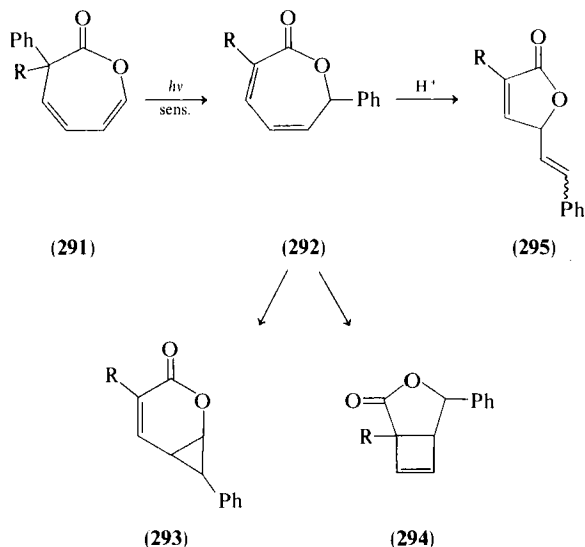
²³⁷ L. Rodriguez-Hahn, M. Jimenez, E. Diaz, C. Guerrero, A. Ortega, and A. Romo de Vivar, *Tetrahedron* **33**, 661 (1977).

²³⁸ K. Maruyama, A. Osuka, and H. Suzuki, *Chem. Lett.*, 1477 (1979).

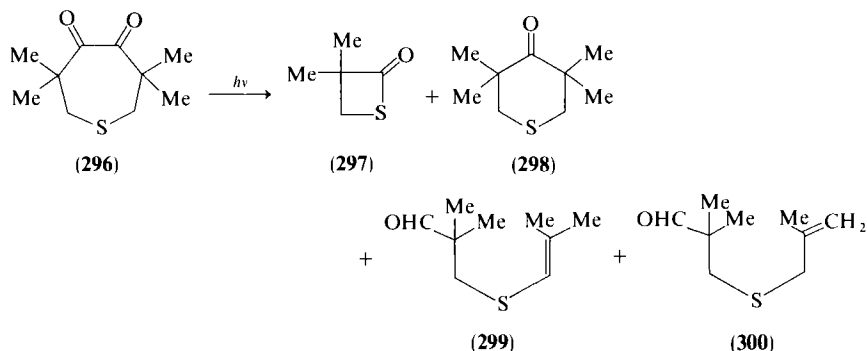
²³⁹ N. Hoshi, H. Hagiwara, and H. Uda, *Chem. Lett.*, 1291 (1979).

²⁴⁰ N. Hoshi, H. Hagiwara, and H. Uda, *Chem. Lett.*, 1295 (1979).

Photorearrangement of aryl-6,7-dioxabicyclo[3.2.2]nona-3,8-dien-2-ones has also been reported.²⁴¹



Apart from electrocyclic transformations, few photoreactions of medium- and large-ring sulfur-containing heterocycles have been described. Thiepin-4-one undergoes ring contraction on irradiation in *tert*-butanol to give γ -thiolactone.²⁴² Ring contraction was also observed in the thiepan-4,5-dione (**296**) on irradiation in benzene and affords the ketones (**297**) and (**298**) together with a low yield of the acyclic sulfides (**299** and **300**).²⁴³ The forma-

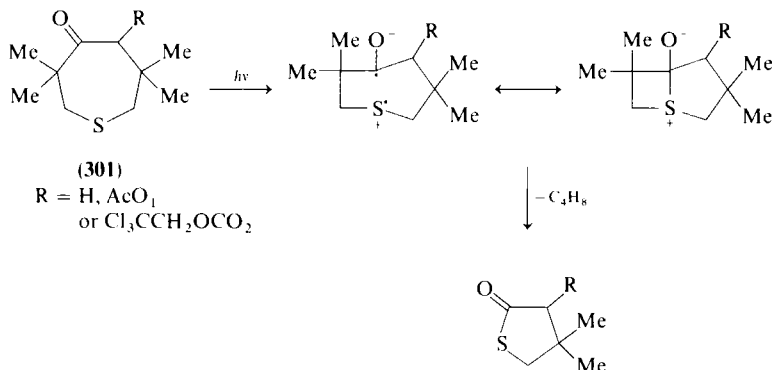


²⁴¹ T. Tezuka, R. Miyamoto, M. Nagayama, and T. Mukai, *Tetrahedron Lett.*, 327 (1975).

²⁴² P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.* **35**, 584 (1970).

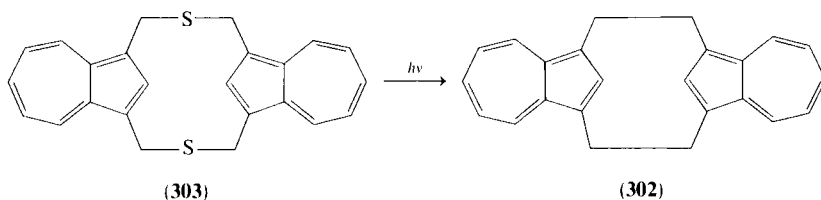
²⁴³ P. Y. Johnson, *Tetrahedron Lett.*, 1991 (1972); J. Kooi, H. Wynberg, and R. M. Kellogg, *Tetrahedron* **29**, 2135 (1973).

tion of these products can be rationalized by an initial α -cleavage, but the reason why this process is not observed in the analogous 3,3,7,7-tetramethylcyclohepta-1,2-dione is not clear. A different explanation, therefore, has been proposed to account for ring contraction in the thiepan-4-ones (**301**); the proposed pathway is shown in Scheme 25.²⁴⁴



SCHEME 25

The photoinduced desulfurization of macrocyclic sulfides in the presence of triethyl phosphite has been widely used in the synthesis of cyclophanes. The [2.2](1,3)-azulenophane (**302**), for example, has been prepared in this way from the 2,13-dithia[3.3]azulenophane (**303**).²⁴⁵ Numerous other



examples of this approach to cyclophanes have been reported.²⁴⁶ The photoreactions of 1,3-dithiepins and 1,3-benzodithiepins have also been studied and appear to involve initial carbon-sulfur bond homolysis.²⁴⁷

²⁴⁴ P. Y. Johnson and M. Berman, *J. Org. Chem.* **40**, 3046 (1975).

²⁴⁵ Y. Fukazawa, M. Aoyagi, and S. Ito, *Tetrahedron Lett.*, 1055 (1979).

²⁴⁶ See, for example, D. Kamp and V. Boekelheide, *J. Org. Chem.* **43**, 3470 (1978); A. Iwama, T. Toyoda, M. Yoshida, T. Otsubo, Y. Sakata, and S. Misumi, *Bull. Chem. Soc. Jpn.* **51**, 2988 (1978); H. Machida, H. Tatemitsu, T. Otsubo, Y. Sakata, and S. Misumi, *ibid.* **53**, 2943 (1980).

²⁴⁷ G. A. Berchtold and R. E. Kohrman, *J. Org. Chem.* **36**, 3971 (1971).

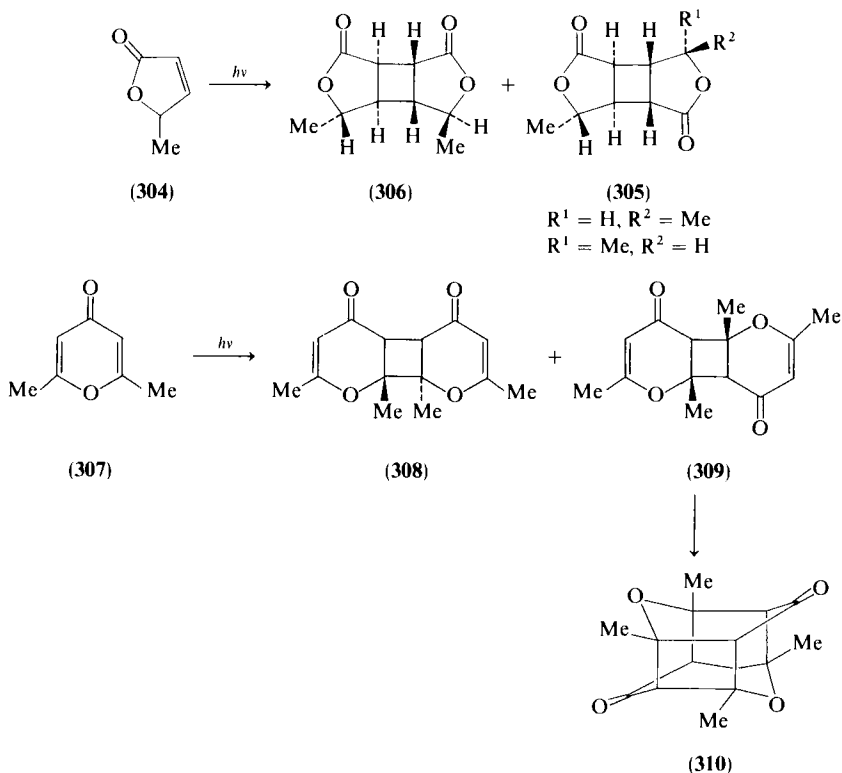
III. Photoaddition

A. PHOTOCYCLOADDITION TO HETEROCYCLES

Intermolecular and intramolecular photocycloadditions to heterocyclic systems, including the photodimerization of individual heterocycles, are considered in this section. Two types of cycloaddition can readily be effected photochemically, namely $[\pi 2 + \pi 2]$ and $[\pi 4 + \pi 4]$.

1. $[\pi 2 + \pi 2]$ Cycloadditions

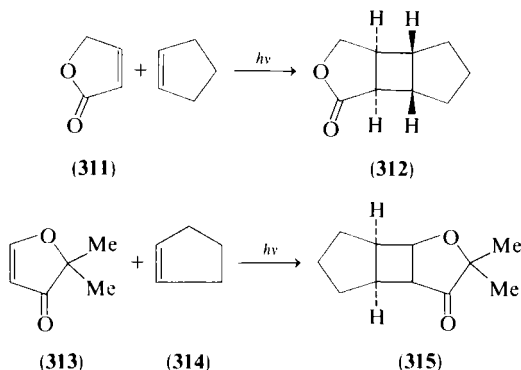
$[\pi 2 + \pi 2]$ Cycloaddition is, in general, an effective way of generating cyclobutane rings. The lactone (304) is converted in this way on irradiation into both head-to-tail (305) and head-to-head (306) dimers.²⁴⁸ Direct irradiation of 5,7-dimethoxycoumarin in acetonitrile or benzene similarly affords the syn head-to-tail dimer via the singlet excited state, whereas



²⁴⁸ K. Ohga and T. Matsuo, *Bull. Chem. Soc. Jpn.* **49**, 1590 (1976).

triplet-sensitized irradiation yields the corresponding anti head-to-tail dimer.²⁴⁹ [$\pi 2 + \pi 2$] Photodimerization has also been reported in, among others, furocoumarin derivatives,²⁵⁰ 2,3-dihydro-2,2,5-trimethylpyran-4-one,²⁵¹ 2,4-dioxo-3,3-dimethyl-2,3-dihydropyran,²⁵² methyl-substituted maleic anhydrides,²⁵³ and 2,6-dimethylpyran-4-one (307), which on irradiation is converted to head-to-head (308) and head-to-tail (309) dimers.²⁵⁴ The cage compound (310) is obtained by further irradiation of 309.

Numerous examples of [$\pi 2 + \pi 2$] photocycloaddition of five-membered oxygen-containing heterocycles to alkenes have been reported, many of which have useful synthetic applications. The regiochemistry and stereochemistry of each adduct has not always been fully established. The lactone (311) undergoes photoaddition to cyclopentene to afford the cis,anti,cis adduct (312), whereas three stereoisomeric adducts were obtained with cyclohexene.²⁵⁵ Analogous additions of substituted lactones to alkenes have been employed in the syntheses of (\pm)-dihydrofomannosin acetate²⁵⁶ and cyclobutane analog of chrysanthemic acid.²⁵⁷ The photoaddition of 2,2-dimethyl-3(2*H*)-furanone (313) to alkenes such as cyclopentene (314) takes place in high yield to afford the adduct (315).²⁵⁸ Further elaboration of these and related adducts has proved useful in synthesis.^{258,259} Cycloaddition of 5-methyl-3(2*H*)-furanone (316) to methyl acrylate, vinyl acetate,



²⁴⁹ S. C. Shim, K. Y. Choi, and P. S. Song, *Photochem. Photobiol.* **27**, 25 (1978).

²⁵⁰ J. Gervais, N. Boens, and F. C. De Schryver, *Nouv. J. Chim.* **3**, 163 (1979).

²⁵¹ X. Duteurtre, J. Lemaire, and R. Vessière, *Bull. Soc. Chim. Fr.*, 911 (1977).

²⁵² P. Margaretha, *Tetrahedron* **27**, 6209 (1971).

²⁵³ P. Boule and J. Lemaire, *J. Chim. Phys. Phys.-Chim. Biol.* **75**, 776 (1978).

²⁵⁴ D. J. MacGregor, *Mol. Photochem.* **6**, 101 (1974).

²⁵⁵ M. Tada, T. Kokubo, and T. Sato, *Tetrahedron* **28**, 2121 (1972).

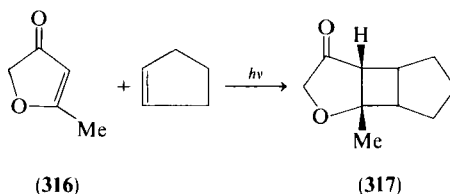
²⁵⁶ H. Kosugi and H. Uda, *Bull. Chem. Soc. Jpn.* **53**, 160 (1980).

²⁵⁷ H.-D. Scharf, J. Janus, and E. Müller, *Tetrahedron* **35**, 25 (1979).

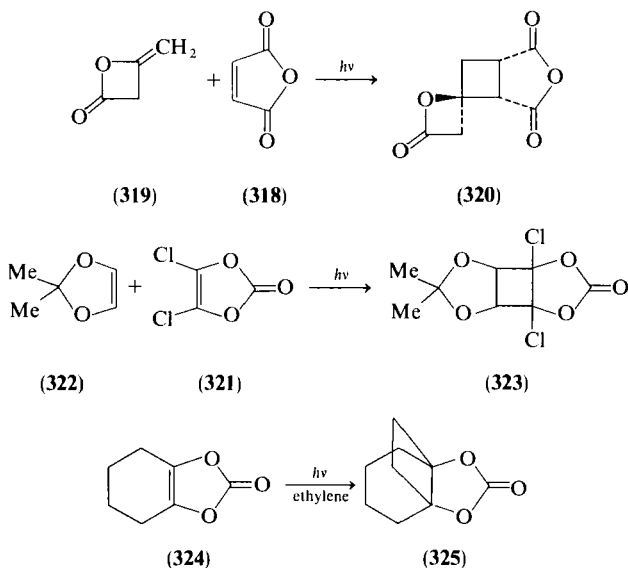
²⁵⁸ S. W. Baldwin and M. T. Crimmins, *Tetrahedron Lett.*, 4197 (1978).

²⁵⁹ S. W. Baldwin and J. M. Wilkinson, *Tetrahedron Lett.*, 2652 (1979); S. W. Baldwin and M. T. Crimmins, *J. Am. Chem. Soc.* **102**, 1198 (1980).

and cyclopentene has been reported on irradiation in benzene²⁶⁰; the adduct (317) was obtained with cyclopentene. Photoaddition of the same furanone to methyl 3-acetoxyprop-2-enoate has been used in the preparation of a key intermediate in the synthesis of 11-deoxyprostaglandin.²⁶¹



New examples of $[\pi_2 + \pi_2]$ photocycloaddition of maleic anhydride (318) to alkenes have been reported.²⁶² The major product of addition to ketene (319), for example, is the spiro cyclobutane (320).²⁶³ The stereoselective addition of dichlorovinylene carbonate to phenanthrene has been described,²⁶⁴ and the photoaddition of this carbonate (321) to the alkene (322)



²⁶⁰ T. Ogina, T. Kubota, and K. Manaka, *Chem. Lett.*, 323 (1976).

²⁶¹ T. Ogina, K. Yamada, and K. Isogai, *Tetrahedron Lett.*, 2445 (1977).

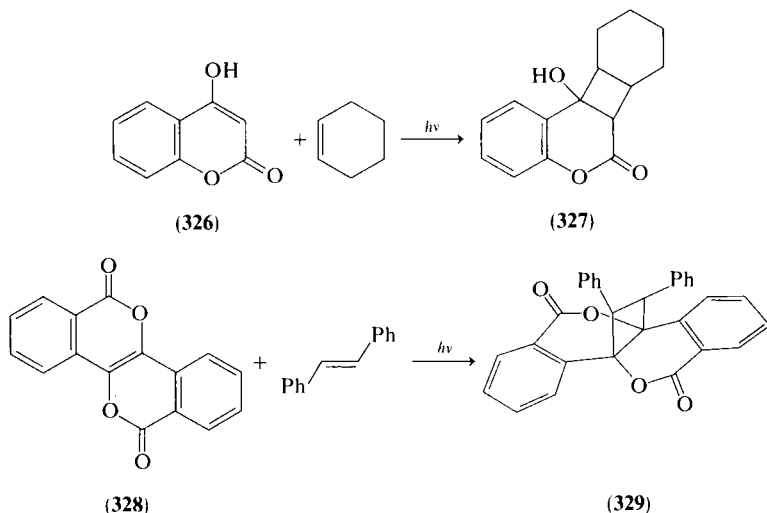
²⁶² W. Hartmann, H.-G. Heine, J. Hinz, and D. Wendisch, *Chem. Ber.* **110**, 2986 (1977); I. Willner and M. Rabinovitz, *Tetrahedron* **35**, 2359 (1979).

²⁶³ T. Kato, T. Chiba, and S. Tsuchiya, *Chem. Pharm. Bull.* **28**, 327 (1980).

²⁶⁴ W. Ried, H. Schinzel, A. H. Schmidt, W. Schuckmann, and H. Fuess, *Chem. Ber.* **113**, 255 (1980).

to give the adduct (323) has been employed in a synthesis of moniliformin.²⁶⁵ A second synthesis of the same cyclobutenedione, but using chlorovinylene carbonate, has been reported,²⁶⁶ and triplet-sensitized cycloaddition of the vinylene carbonate (324) to ethylene affords the propellane (325).²⁶⁷ The photochemically induced cycloaddition reactions of cyclic oxa-enones have been reviewed.²⁶⁸

Addition to six-membered oxygen heterocycles is also common. The photocycloaddition of 5,7-dimethoxycoumarin to tetramethylethylene has been described,²⁶⁹ and 4-hydroxycoumarin (326) undergoes facile addition to cyclohexene on direct irradiation to give the cyclobutane (327)²⁷⁰; analogous additions to a variety of other alkenes have been reported, and the cycloaddition of 4-methoxycoumarin to 2-methylpropene has been employed in a synthesis of 1,2-dihydrocyclobuta[*c*]coumarin.²⁷¹ Photoaddition of the 1,2-bis-enol lactone (328) to *trans*-stilbene yields propellane (329),²⁷² and $[\pi 2 + \pi 2]$ cycloaddition is observed along with other competing photoreactions on irradiation of chromone in the presence of alkenes.²⁷³



²⁶⁵ D. Bellus, H. Fischer, H. Greuter, and P. Martin, *Helv. Chim. Acta* **61**, 1784 (1978).

²⁶⁶ H.-D. Sharf, H. Frauenrath, and W. Pinske, *Chem. Ber.* **111**, 168 (1978).

²⁶⁷ H.-M. Fischler, H.-G. Heine, and W. Hartmann, *Tetrahedron Lett.*, 1701 (1972).

²⁶⁸ P. Margaretha, *Chimia* **29**, 203 (1975).

²⁶⁹ S. C. Shim and D. Y. Chi, *Chem. Lett.*, 1229 (1978).

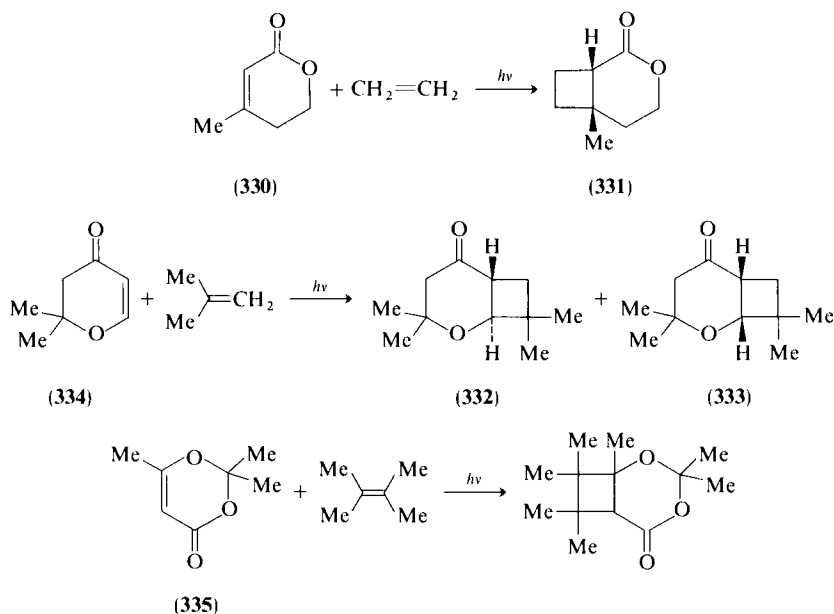
²⁷⁰ D. J. Haywood, R. G. Hunt, C. J. Potter, and S. T. Reid, *J. C. S. Perkin I*, 2458 (1977).

²⁷¹ T. Naito, N. Nakayama, and C. Kaneko, *Chem. Lett.*, 423 (1981).

²⁷² G. Kaupp and D. Schmitt, *Chem. Ber.* **114**, 1983 (1981).

²⁷³ J. W. Hanifin and E. Cohen, *J. Am. Chem. Soc.* **91**, 4494 (1969).

The photoaddition of the pyran-2-one (330) to ethylene to give the adduct (331) has been employed in a synthesis of grandisol,²⁷⁴ and the cyclobutane derivatives (332 and 333) were obtained on irradiation of the pyran-4-one (334) in 2-methylpropene.²⁷⁵ Photocycloadditions of dehydroacetic acid²⁷⁶ and 2,4-dioxo-3,3-dimethyl-2,3-dihydropyran²⁷⁷ have also been described, and the synthetically useful addition of 2,2,6-trimethyl-1,3-dioxolenone (335) to 2,3-dimethylbut-2-ene has been reported.²⁷⁸



$[\pi 2 + \pi 2]$ Photocycloaddition of oxygen heterocycles to alkynes has been of some use in the preparation of cyclobutene derivatives.²⁷⁹ Irradiation of tetrakis(trifluoromethyl)furan (336) and dimethylacetylene, for example, affords the adduct (337), which on further irradiation, is converted to the cage isomer (338).²⁸⁰

²⁷⁴ R. C. Gueldner, A. C. Thompson, and P. A. Hedin, *J. Org. Chem.* **37**, 1854 (1972).

²⁷⁵ P. Margaretha, *Justus Liebigs Ann. Chem.*, 727 (1973).

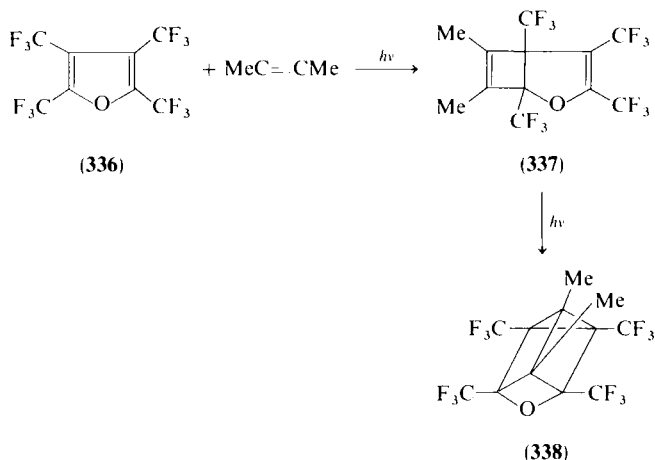
²⁷⁶ H. Takeshita, R. Kikuchi, and Y. Shoji, *Bull. Chem. Soc. Jpn.* **46**, 690 (1973).

²⁷⁷ P. Margaretha, *Tetrahedron* **27**, 6209 (1971).

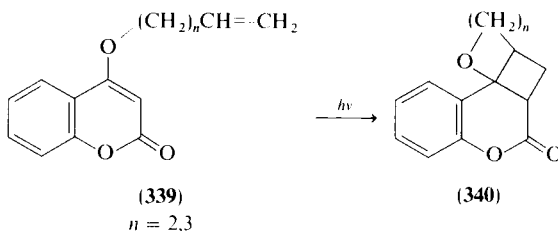
²⁷⁸ S. W. Baldwin and J. M. Wilkinson, *J. Am. Chem. Soc.* **102**, 3634 (1980).

²⁷⁹ M. P. Servé and H. M. Rosenberg, *J. Org. Chem.* **35**, 1237 (1970); R. H. Grubbs, *J. Am. Chem. Soc.* **92**, 6693 (1970); J. W. Hanifin and E. Cohen, *J. Org. Chem.* **36**, 910 (1971); J. C. Hinshaw, *J. C. S. Chem. Commun.*, 630 (1971); A. H. A. Tinnemans and D. C. Neckers, *J. Org. Chem.* **42**, 2374 (1977).

²⁸⁰ Y. Kobayashi and Y. Hanzawa, *Tetrahedron Lett.*, 4301 (1978).



Intramolecular [$\pi 2 + \pi 2$] photocycloadditions have been observed in 7,7-polymethylenedioxycoumarins²⁸¹ and in 4-alkenoxycoumarins (339), which on irradiation are converted to the cyclobutane derivatives (340).²⁸²



The unsaturated lactones (341) behave in a similar fashion and yield the isomers (342).²⁸³ The formation of the oxygen-bridged quadricyclane (343) is a consequence of intramolecular addition in 7-oxa-norbornadiene (344)²⁸⁴; many analogous transformations have been reported in substituted 7-oxanorbornadienes²⁸⁵ and in 1,4-epoxy-1,4-dihydronaphthalenes,²⁸⁶ which are further converted to benzoxepins.

²⁸¹ F. C. De Schryver, J. Put, L. Leenders, and H. Loos, *J. Am. Chem. Soc.* **96**, 6994 (1974).

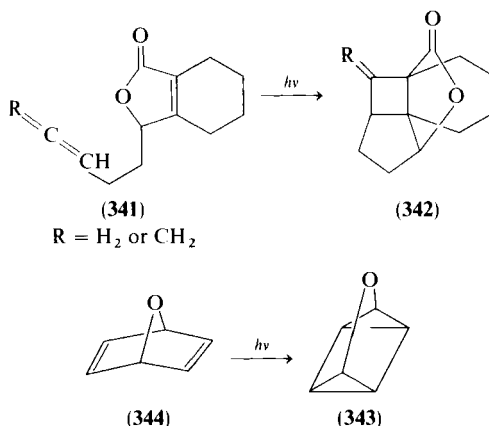
²⁸² D. J. Haywood and S. T. Reid, *Tetrahedron Lett.*, 2637 (1979).

²⁸³ W. R. Baker, P. D. Senter, and R. M. Coates, *J. C. S. Chem. Commun.*, 1011 (1980).

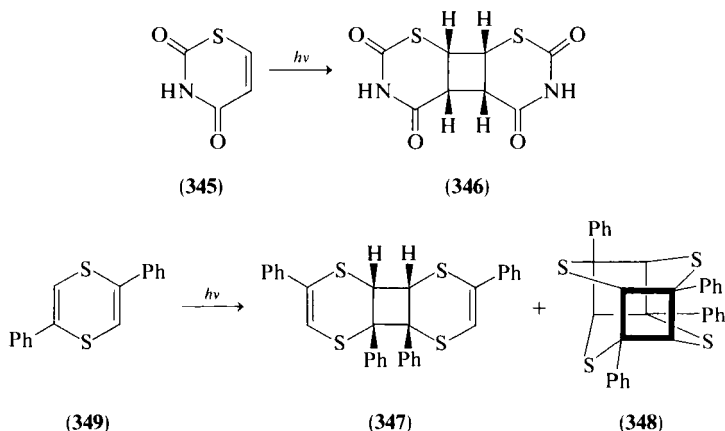
²⁸⁴ H. Prinzbach and H. Babsch, *Angew. Chem., Int. Ed. Engl.* **14**, 753 (1975).

²⁸⁵ R. Hogeveen and B. J. Nüsse, *Tetrahedron Lett.*, 699 (1976); W. Eberbach, M. Perroud-Arguelles, H. Achenbach, E. Druchrey, and H. Prinzbach, *Helv. Chim. Acta* **54**, 2579 (1971); W. Tochtermann and H. Timm, *Tetrahedron Lett.*, 2145 (1978).

²⁸⁶ G. R. Ziegler, *J. Am. Chem. Soc.* **91**, 446 (1969); H. Prinzbach, H. Babsch, H. Fritz, and P. Hug, *Tetrahedron Lett.*, 1355 (1977); R. A. F. Matheson, A. W. McCulloch, A. G. McInnes, and D. G. Smith, *Can. J. Chem.* **55**, 1422 (1977); W. Tochtermann, H. Timm, and J. Dickmann, *Tetrahedron Lett.*, 4311 (1977).



[$\pi 2 + \pi 2$] Photodimerizations have been observed in a variety of sulfur-containing heterocycles; notable examples include the photodimerization of 2- and 3-arylbenzo[*b*]thiophenes,²⁸⁷ benzo[*b*]thiophen 1-oxide,²⁸⁸ benzo[*b*]thiophen 1,1-dioxide,²⁸⁹ and its 2-bromo²⁸⁹ and 2-methyl derivatives.²⁹⁰ All four possible dimers were obtained on irradiation of thiochromone in aromatic solvents,²⁹¹ and 1-thiauracil (345) is converted into



²⁸⁷ A. Buquet, A. Couture, A. Lablache-Combiér, and A. Pollet, *Tetrahedron* **37**, 75 (1981).

²⁸⁸ M. S. El Faghi El Amoudi, P. Geneste, and J. L. Olivé, *Tetrahedron Lett.*, 999 (1978).

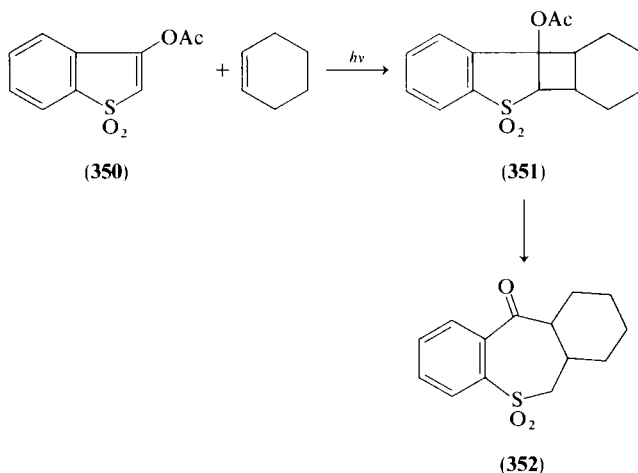
²⁸⁹ W. W. Schloman and B. F. Plummer, *J. Am. Chem. Soc.* **98**, 3254 (1976).

²⁹⁰ M. J. Hopkinson, W. W. Schloman, B. F. Plummer, E. Wenkert, and M. Ragu, *J. Am. Chem. Soc.* **101**, 2157 (1979).

²⁹¹ I. W. J. Still and T. S. Leong, *Tetrahedron Lett.*, 1183 (1981).

the *cis,syn,cis* dimer (**346**) on irradiation in the solid state.²⁹² A head-to-tail dimer was formed on irradiation of 2,6-dimethylthiopyran-4-one,²⁹³ whereas the dimer (**347**) and the cage compound (**348**) were obtained by irradiation of 2,5-diphenyl-1,4-dithiin (**349**) in diethyl ether.²⁹⁴

The cycloaddition of a variety of sulfur heterocycles to alkenes has also been reported. Dibromomaleic anhydride undergoes $[\pi 2 + \pi 2]$ cycloaddition to thiophen²⁹⁵ and to benzo[*b*]thiophen.²⁹⁶ The photoaddition of benzo[*b*]thiophen 1,1-dioxides to alkenes also affords cyclobutane derivatives.²⁹⁷ Of particular interest is the addition of 3-acetoxybenzo[*b*]thiophen (**350**) to cyclohexene to give the adduct (**351**), which on treatment with base, undergoes a "retro-aldol" ring opening to benzo[*b*]thiepinone (**352**).²⁹⁸ A mixture of stereoisomeric cyclobutane derivatives were obtained on irradiation of 2,6-diphenyl-4*H*-thiopyran-4-one 1,1-dioxide in cyclohexene.²⁹⁹ The $[\pi 2 + \pi 2]$ cycloaddition of sulfolen to maleic anhydride and to maleimide has been reported.³⁰⁰



²⁹² J. B. Bremner, R. N. Warrenner, E. Adman, and L. H. Jensen, *J. Am. Chem. Soc.* **93**, 4574 (1971).

²⁹³ N. Ishibe and M. Odani, *J. Org. Chem.* **36**, 4132 (1971).

²⁹⁴ K. Kobayashi and T. Ohi, *Chem. Lett.*, 645 (1973).

²⁹⁵ H. Wamhoff and H.-J. Hupe, *Tetrahedron Lett.*, 125 (1978).

²⁹⁶ T. Matsuo and S. Mihara, *Bull. Chem. Soc. Jpn.* **50**, 1797 (1977).

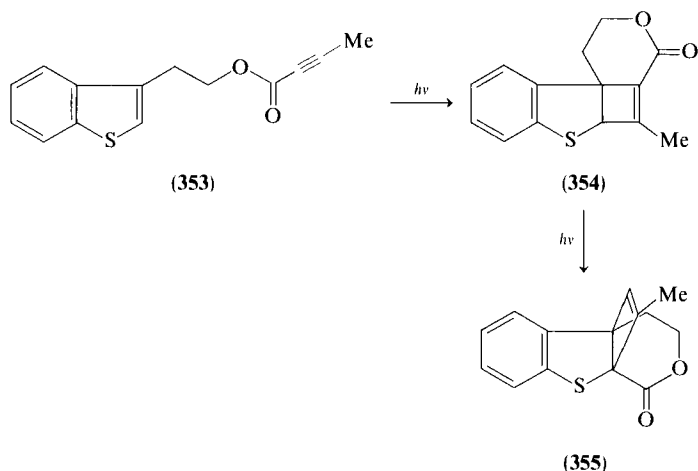
²⁹⁷ D. N. Harpp and C. Heitner, *J. Org. Chem.* **38**, 4184 (1973).

²⁹⁸ N. V. Kirby and S. T. Reid, *J. C. S. Chem. Commun.*, 150 (1980).

²⁹⁹ H. Aoyama, Y. Sato, T. Nishio, and N. Sugiyama, *Bull. Chem. Soc. Jpn.* **46**, 1007 (1973).

³⁰⁰ V. Sh. Shaikhrazieva, R. S. Enikeev, and G. A. Tolstikov, *Zh. Org. Khim.* **7**, 1763 (1971).

A number of examples of photoaddition to alkynes has been described. Dimethyl acetylenedicarboxylate has been found to add to methyl-substituted 3-benzoylthiophenes³⁰¹ and to thiophen and 2,5-dimethylthiophen³⁰² on irradiation. Benzo[*b*]thiophen also undergoes cycloaddition reactions with alkynes,³⁰³ and in the case of dimethylacetylene dicarboxylate, product formation has been shown to be wavelength dependent.³⁰⁴ Intramolecular [$\pi 2 + \pi 2$] cycloaddition has been observed on both direct and triplet-sensitized irradiation of the alkyne (353) and gives the cyclobutene (354)³⁰⁵; the isomer (355) is formed on prolonged irradiation.



In certain cases benzene will undergo photocycloaddition to oxygen and sulfur heterocycles. The two major photoproducts of irradiation of a mixture of furan and benzene are adducts 356 and 357, arising, respectively, by [$\pi 2 + \pi 2$] and [$\pi 4 + \pi 4$] cycloaddition processes.³⁰⁶ Irradiation of benzene and 2,2-dimethyl-1,3-dioxol (358) similarly affords adducts 359 and 360, together with dimer 361.³⁰⁷ Thiochromone 1,1-dioxide also undergoes photoaddition to benzene.³⁰⁸

³⁰¹ D. R. Arnold and C. P. Hadjiantoniou, *Can. J. Chem.* **56**, 1920 (1978).

³⁰² H. J. Kuhn and K. Gollnick, *Chem. Ber.* **106**, 674 (1973).

³⁰³ J. H. Dopfer and D. C. Neckers, *J. Org. Chem.* **36**, 3755 (1971).

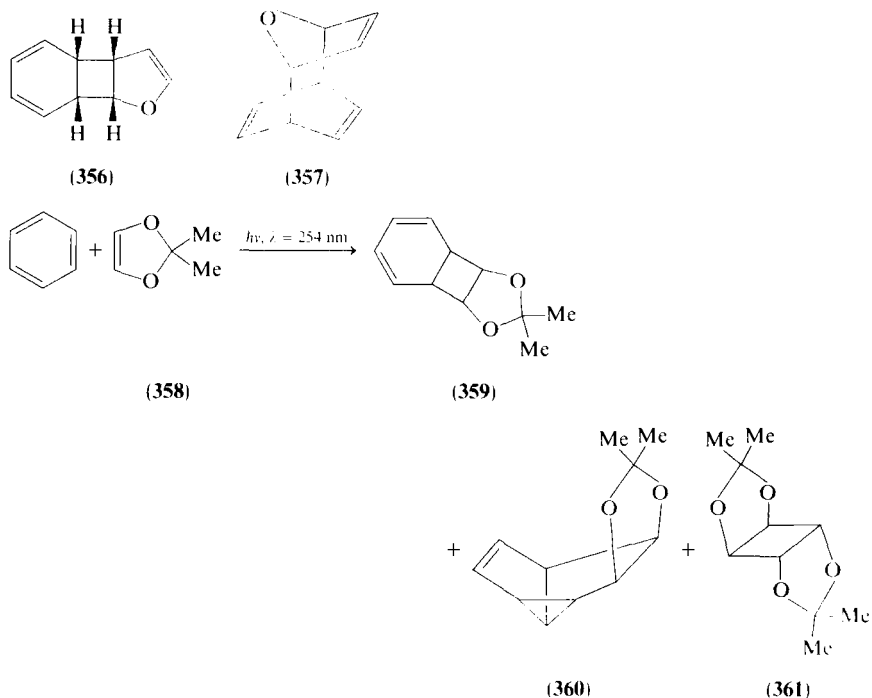
³⁰⁴ S. R. Ditto, P. D. Davis, and D. C. Neckers, *Tetrahedron Lett.*, 521 (1981).

³⁰⁵ A. H. A. Tinnemans and D. C. Neckers, *J. Org. Chem.* **43**, 2493 (1978).

³⁰⁶ J. C. Berridge, A. Gilbert, and G. N. Taylor, *J. C. S. Perkin I*, 2174 (1980).

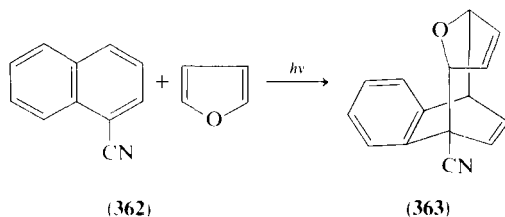
³⁰⁷ J. Mattay, H. Leismann, and H.-D. Scharf, *Chem. Ber.* **112**, 577 (1979).

³⁰⁸ I. J. W. Still and T. S. Leong, *Tetrahedron Lett.*, 1097 (1979).



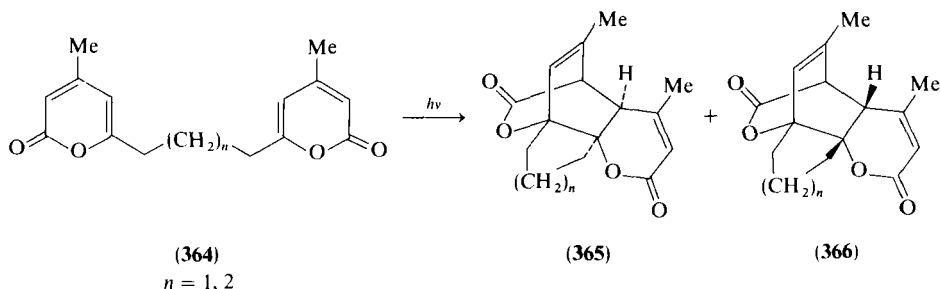
2. [$\pi 4 + \pi 4$] Cycloadditions

There are few new authenticated examples of [$\pi 4 + \pi 4$] photoadditions in oxygen- and sulfur-containing heterocycles. 1-Cyanonaphthalene (**362**), for example, undergoes an addition of this type to furan on irradiation in benzene to give adduct **363** in high yield.³⁰⁹ Addition of 2-cyanonaphthalene



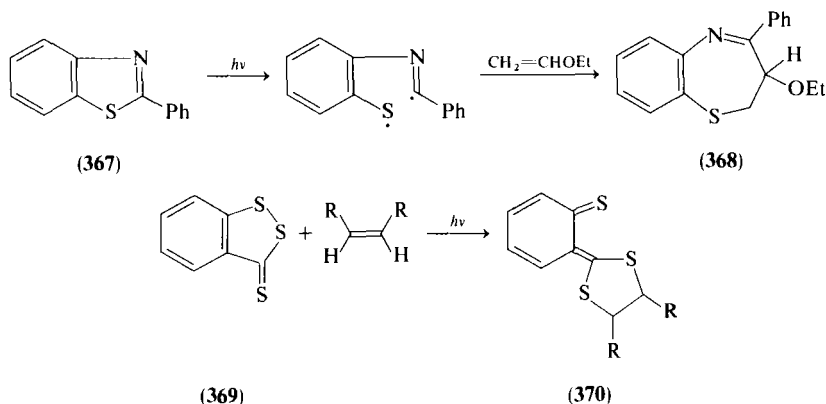
³⁰⁹ C. Pac, T. Sugioka, and H. Sakurai, *Chem. Lett.*, 39 (1972).

to furan has also been reported.³¹⁰ [$\pi 4 + \pi 2$] Photocycloaddition is sometimes preferred in situations in which [$\pi 4 + \pi 4$] addition might be expected. Thus, [$4 + 2$] adducts were obtained on irradiation of diphenylisobenzofuran in 1,4-diphenylbutadiene.³¹¹ Similarly, the bispyrones (**364**) on triplet-sensitized irradiation undergo intramolecular [$\pi 4 + \pi 2$] cycloaddition to give the tetracyclic photoproducts (**365** and **366**).³¹²



3. Miscellaneous Cycloadditions

A number of cycloadditions have been shown to arise by initial bond homolysis in the heterocycle followed by the addition of the resulting biradical to an alkene. The photoaddition of 2-phenylbenzothiazole (**367**) to ethyl vinyl ether to give the 1,5-benzothiazepine (**368**) can be interpreted in this way.³¹³ Similar pathways have been proposed to account for the



³¹⁰ T. Sugioka, C. Pac, and H. Sakurai, *Chem. Lett.*, 791 (1972).

³¹¹ G. Kaupp and E. Teufel, *J. Chem. Res., Synop.*, 100 (1978).

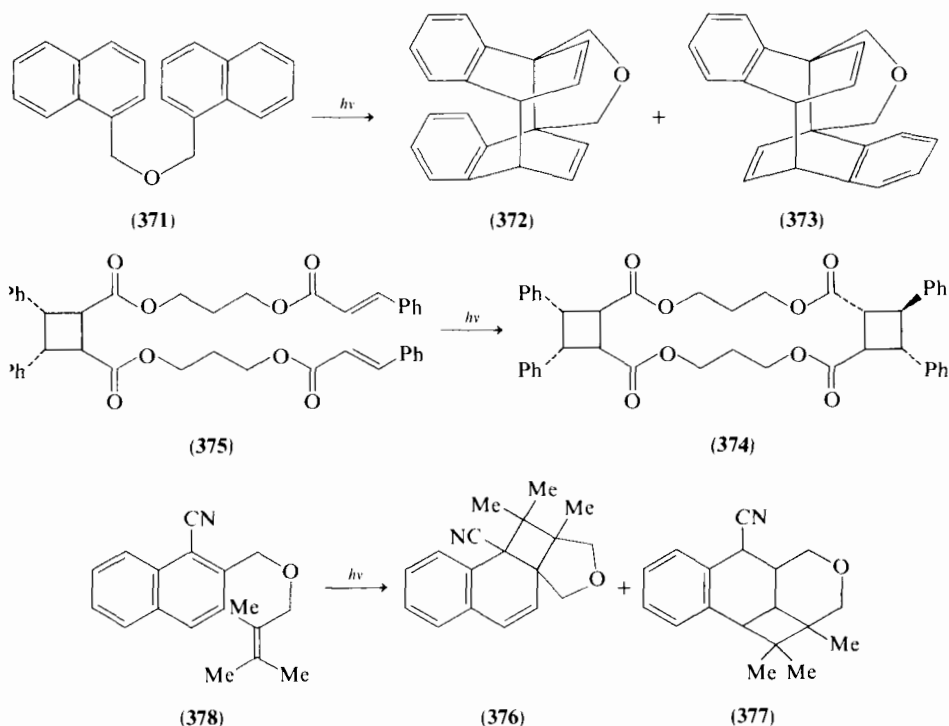
³¹² M. van Meerbeck, S. Toppet, and F. C. de Schryver, *Tetrahedron Lett.*, 2247 (1972).

³¹³ M. Sindler-Kulyk and D. C. Neckers, *Tetrahedron Lett.*, 2081 (1981).

photoaddition of 3-phenyl-1,2-benzothiazole to ethyl vinyl ether³¹⁴ and to account for the addition of 1,2-benzodithiole-3-thione (**369**) to alkenes to give the deep-blue *o*-thioquinone methides (**370**).³¹⁵

B. SYNTHESIS OF HETEROCYCLES BY PHOTOADDITION

A variety of cycloaddition processes have been employed in the synthesis of oxygen and sulfur heterocycles. Intramolecular [$\pi 4 + \pi 4$] and [$\pi 2 + \pi 2$] additions in suitably designed molecules, for example, have proved useful in this connection. Di-(α -naphthylmethyl)ether (**371**) is converted in this way to adducts **372** and **373**,³¹⁶ and similar transformations have been

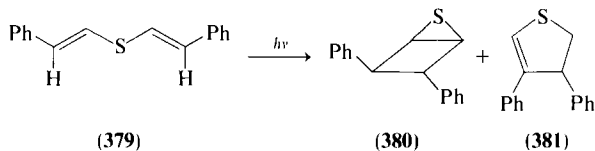


³¹⁴ M. Sindler-Kulyk and D. C. Neckers, *Tetrahedron Lett.*, 529 (1981).

³¹⁵ R. Okazaki, K. Sunagawa, K.-T. Kang, and N. Inamoto, *Bull. Chem. Soc. Jpn.* **52**, 496 (1979).

³¹⁶ R. Todesco, J. Gelan, H. Martens, J. Put, N. Boens, and F. C. de Schryver, *Tetrahedron Lett.*, 2815 (1978).

reported in oxygen-linked bisanthracenes.³¹⁷ The macrocyclic lactone (374) has been prepared from the dicinnamate (375) by an intramolecular [$\pi 2 + \pi 2$] cycloaddition process³¹⁸; the cyclobutanes (376 and 377) have similarly been obtained by irradiation of the unsaturated ether (378).³¹⁹ Other analogous transformations have been reported.³²⁰ The divinyl sulfide (379) is photochemically converted to the thiiran (380) and dihydrothiophen (381).³²¹



The cycloaddition of carbonyl-containing compounds to alkenes to yield oxetans (the Paterno–Buchi reaction) was one of the first photoreactions to be described in the literature. The study of the mechanism and synthetic applications³²² of this process continues to attract widespread attention, and numerous papers have been published during the period covered by this report. Although competing photoreactions and energy transfer processes are often observed in such investigations, the reaction provides a valuable route to oxetan-containing systems.

The photoaddition of simple aldehydes and ketones to alkenes,³²³ electron-deficient alkenes,³²⁴ electron-rich alkenes,³²⁵ and carbohydrate-

³¹⁷ J.-P. Desvergne and H. Bouas-Laurent, *J. C. S. Chem. Commun.*, 403 (1978); *Isr. J. Chem.* **18**, 220 (1979); I. Yamashita, M. Fujii, T. Kaneda, S. Misumi, and T. Otsubo, *Tetrahedron Lett.*, 541 (1980).

³¹⁸ J. A. Ors and R. Srinivasan, *J. Am. Chem. Soc.* **100**, 315 (1978).

³¹⁹ J. J. McCullough, W. K. MacInnis, C. J. L. Lock, and R. Faggiani, *J. Am. Chem. Soc.* **102**, 7780 (1980).

³²⁰ J. Rokach, Y. Girard, and J. G. Atkinson, *J. C. S. Chem. Commun.*, 602 (1975); Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, *J. Org. Chem.* **40**, 2702 (1975); A. Gilbert and G. Taylor, *J. C. S. Chem. Commun.*, 129 (1978).

³²¹ E. Block and E. J. Corey, *J. Org. Chem.* **34**, 896 (1969).

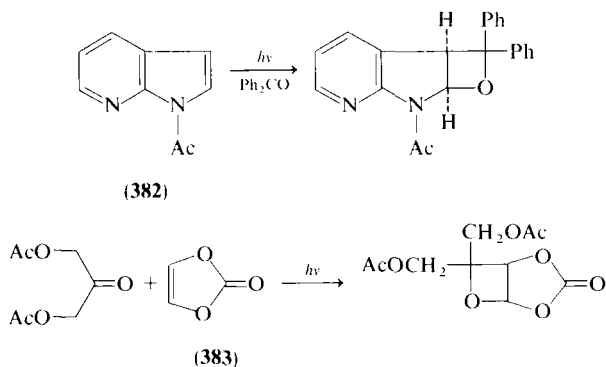
³²² G. Jones, *Org. Photochem.* **5**, 1 (1981).

³²³ N. C. Yang, M. Kimura, and W. Eisenhardt, *J. Am. Chem. Soc.* **95**, 5058 (1973); H. A. J. Carless, *J. C. S. Perkin II*, 834 (1974); N. Shimizu, M. Ishikawa, K. Ishikura, and S. Nishida, *J. Am. Chem. Soc.* **96**, 6456 (1974); H. A. J. Carless and H. S. Trivedi, *J. C. S. Chem. Commun.*, 581 (1975); A. A. Gorman, R. L. Leyland, C. T. Parekh, and M. A. J. Rodgers, *Tetrahedron Lett.*, 1391 (1976); M. Nitta, H. Sugiyama, and Y. Sekine, *Chem. Lett.*, 55 (1977); H. Ruotsalainen, *Acta Chem. Scand., Ser. B* **32**, 417 (1978); M. G. Barlow, B. Coles, and R. N. Haszeldine, *J. C. S. Perkin I*, 2258 (1980).

³²⁴ J. C. Dalton, P. A. Wriede, and N. J. Turro, *J. Am. Chem. Soc.* **92**, 1318 (1970); J. A. Barltrop and H. A. J. Carless, *ibid.* **94**, 1951 (1972).

³²⁵ S. H. Schroeter and C. M. Orlando, *J. Org. Chem.* **34**, 1181 (1969); N. J. Turro and P. A. Wriede, *J. Am. Chem. Soc.* **92**, 320 (1970); N. E. Schore and N. J. Turro, *ibid.* **97**, 2482 (1975).

derived alkenes³²⁶ has been reported. Low-temperature irradiation of acetone leads to the formation of the two oxetans derived by photocycloaddition of acetone to its enol.³²⁷ Particular attention has been paid to the photoaddition of ketones to unsaturated heterocycles leading to the formation of fused oxetans; additions of this type to uracil and cytosine,³²⁸ pyrroles,³²⁹ imidazoles,³³⁰ *N*-acylindoles,³³¹ the 7-azaindole (**382**),³³² benzofuran,³³³ 2,6-dioxabicyclo[3.2.0]heptane,³³⁴ and 1,3-dioxol-2-one (**383**)³³⁵ have been reported.



Seven stereoisomeric and regioisomeric vinyloxetans (**384** to **390**) were obtained on photoaddition of acetaldehyde to (*E*)- or (*Z*)-penta-1,3-diene.³³⁶ Other instances of [2 + 2] photoaddition of ketones to conjugated dienes have been described.³³⁷ Iminooxetans are similarly prepared by addition of carbonyl-containing compounds to ketenimines.³³⁸

³²⁶ K.-S. Ong and R. L. Whistler, *J. Org. Chem.* **37**, 572 (1972); K. Matsuura, Y. Araki, and Y. Ishido, *Bull. Chem. Soc. Jpn.* **45**, 3496 (1972); K. Matsuura, Y. Araki, Y. Ishido, and A. Murai, *Carbohydr. Res.* **29**, 459 (1973).

³²⁷ A. Henne and H. Fischer, *Helv. Chim. Acta* **58**, 1598 (1975).

³²⁸ A. J. Varghese, *Photochem. Photobiol.* **21**, 147 (1975).

³²⁹ C. Rivas and R. A. Bolivar, *J. Heterocycl. Chem.* **13**, 1037 (1976).

³³⁰ T. Nakano, C. Rivas, C. Perez, and J. M. Larrauri, *J. Heterocycl. Chem.* **13**, 173 (1976).

³³¹ D. R. Julian and G. D. Tringham, *J. C. S. Chem. Commun.*, 13 (1973).

³³² T. Nakano and M. Santana, *J. Heterocycl. Chem.* **13**, 585 (1976).

³³³ S. Farid, S. E. Hartman, and C. D. De Boer, *J. Am. Chem. Soc.* **97**, 808 (1975).

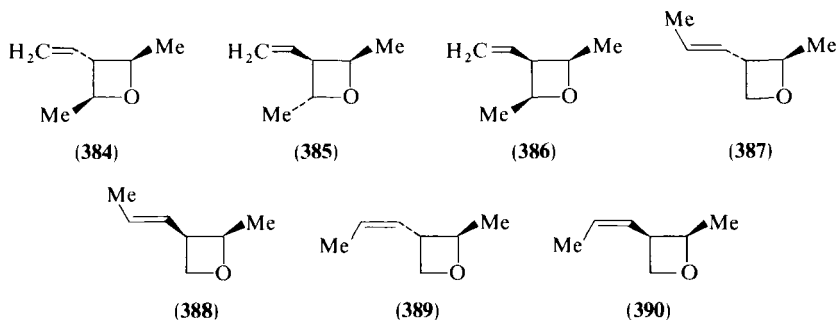
³³⁴ H. A. J. Carless and D. J. Haywood, *J. C. S. Chem. Commun.*, 1067 (1980).

³³⁵ Y. Araki, J. Nagasawa, and Y. Ishido, *J. C. S. Perkin I*, 12 (1981).

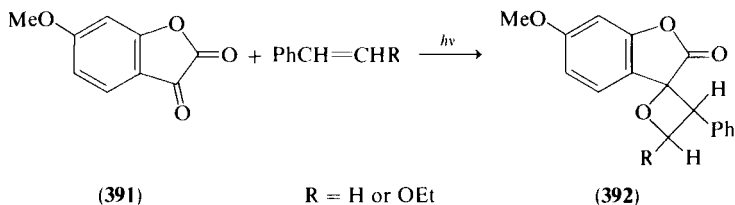
³³⁶ H. A. J. Carless and A. K. Maitra, *Tetrahedron Lett.*, 1411 (1977).

³³⁷ P. Dowd, A. Gold, and K. Sachdev, *J. Am. Chem. Soc.* **92**, 5724 (1970); J. A. Barltrop and H. A. J. Carless, *ibid.* **94**, 8761 (1972); R. R. Hautala, K. Dawes, and N. J. Turro, *Tetrahedron Lett.*, 1229 (1972); C. W. Funke and H. Cerfontain, *J. C. S. Perkin II*, 1902 (1976); K. Shima, T. Kubota, and H. Sakurai, *Bull. Chem. Soc. Jpn.* **49**, 2567 (1976).

³³⁸ L. A. Singer, G. A. Davis, and R. L. Knutsen, *J. Am. Chem. Soc.* **94**, 1188 (1972); K. Ogina, S. Yamashina, T. Matsumoto, and S. Kozuka, *J. C. S. Perkin I*, 1552 (1979); K. Ogina, T. Matsumoto, T. Kawai, and S. Kozuka, *J. Org. Chem.* **44**, 3352 (1979).



Variation in the carbonyl component has also been reported. Irradiation of 6-methoxybenzo[*b*]furan-2,3-dione (**391**) in the presence of styrene or *β*-ethoxystyrene affords adducts **392**.³³⁹ Other 1,2-dicarbonyl compounds



undergo analogous additions to alkenes,³⁴⁰ as do a variety of α,β -unsaturated ketones,³⁴¹ *p*-benzoquinones,³⁴² and heterocyclic ketones such as 3-benzoylthiophene (**393**).³⁴³ Surprisingly, perhaps, certain esters also undergo photoaddition to alkenes to give alkoxyoxetans.³⁴⁴ Irradiation of the carbamates (**394**) in 1,1-diphenylethylene (**395**), for example, give the oxetans (**396**).³⁴⁵ Analogous additions have been reported with aroyl halides³⁴⁶ and with anhydrides.³⁴⁷

³³⁹ T. I. Gray, A. Pelter, and R. S. Ward, *Tetrahedron* **35**, 2539 (1979).

³⁴⁰ R. R. Sauers, P. C. Valenti, and E. Tauss, *Tetrahedron Lett.*, 3129 (1975); W. Friedrichsen, *Justus Liebigs Ann. Chem.*, 1545 (1975); K. Shima, S. Takeo, K. Yakoyama, and H. Yamaguchi, *Bull. Chem. Soc. Jpn.* **50**, 761 (1977).

³⁴¹ P. M. Collins and B. R. Whitton, *J. C. S. Perkin I*, 1470 (1973); Z. Yoshida, M. Kimura, and S. Yoneda, *Tetrahedron Lett.*, 1001 (1975); G. V. Thi and P. Margaretha, *Helv. Chim. Acta* **59**, 2236 (1976).

³⁴² N. J. Bunce and M. Hadley, *Can. J. Chem.* **53**, 3240 (1975); H. Inoue, A. Ezaki, H. Tomono, and M. Hida, *J. C. S. Chem. Commun.*, 860 (1979); K. Ogina, T. Matsumoto, and S. Kozuka, *ibid.*, 643.

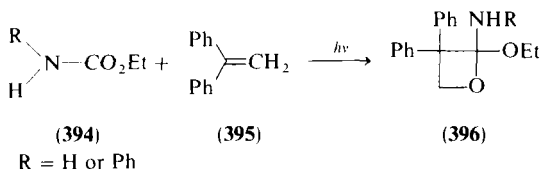
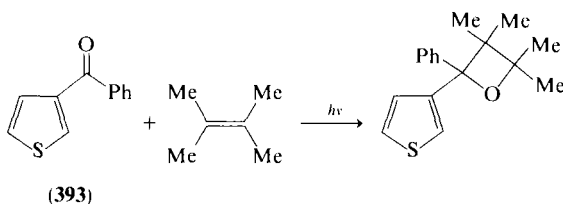
³⁴³ T. S. Cantrell, *J. Org. Chem.* **42**, 3774 (1977).

³⁴⁴ Y. Shigemitsu, Y. Katsuhara, and Y. Odaira, *Tetrahedron Lett.*, 2887 (1971); T. S. Cantrell, *J. C. S. Chem. Commun.*, 468 (1973); S. Farid, S. E. Hartman, J. C. Doty, and J. L. R. Williams, *J. Am. Chem. Soc.* **97**, 3697 (1975).

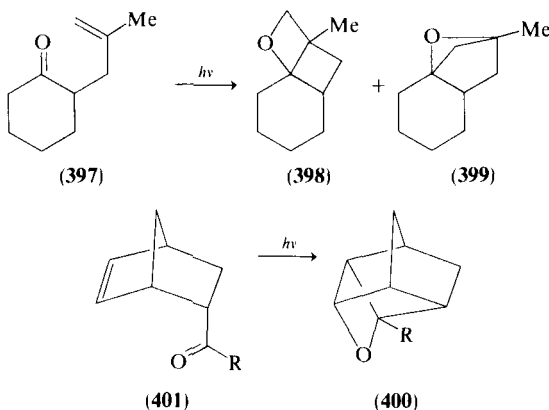
³⁴⁵ T. Tominaga and S. Tsutsumi, *Tetrahedron Lett.*, 3175 (1969).

³⁴⁶ T. S. Cantrell, *J. C. S. Chem. Commun.*, 637 (1975).

³⁴⁷ K. Maruyama, T. Ogawa, and Y. Kubo, *Chem. Lett.*, 343 (1980).



Intramolecular cycloaddition, particularly in γ,δ -unsaturated ketones,³⁴⁸ has also been reported. Recent examples include the photochemically induced conversion of the cyclohexanone (397) to the two possible adducts (398 and 399)³⁴⁹ and the formation of the oxetans (400) from 5-aclynorbornenes (401).³⁵⁰ The introduction of an ether oxygen into the unsaturated ketone



provides a route to fused dioxetans, as shown for ketone 402 in Scheme 26.³⁵¹ Rearrangement and intramolecular photocycloaddition were observed in 1-cyclopentenylloxypentan-2-one.³⁵² Intramolecular photocycloaddition

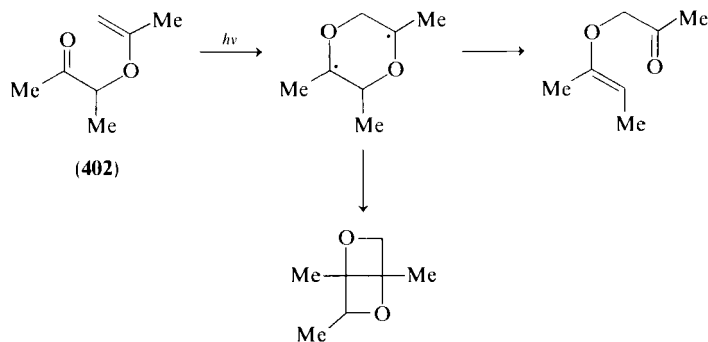
³⁴⁸ S. R. Kurowsky and H. Morrison, *J. Am. Chem. Soc.* **94**, 507 (1972); J. K. Crandall and C. F. Mayer, *J. Org. Chem.* **34**, 2814 (1969); J. Meinwald and A. T. Hammer, *J. C. S. Chem. Commun.*, 1302 (1969).

³⁴⁹ J. Kossanyi, P. Jost, B. Furth, G. Daccord, and P. Chaquin, *J. Chem. Res., Synop.*, 368 (1980).

³⁵⁰ R. R. Sauers, A. D. Rousseau, and B. Byrne, *J. Am. Chem. Soc.* **97**, 4947 (1975); R. R. Sauers and B. Byrne, *J. Org. Chem.* **45**, 1286 (1980).

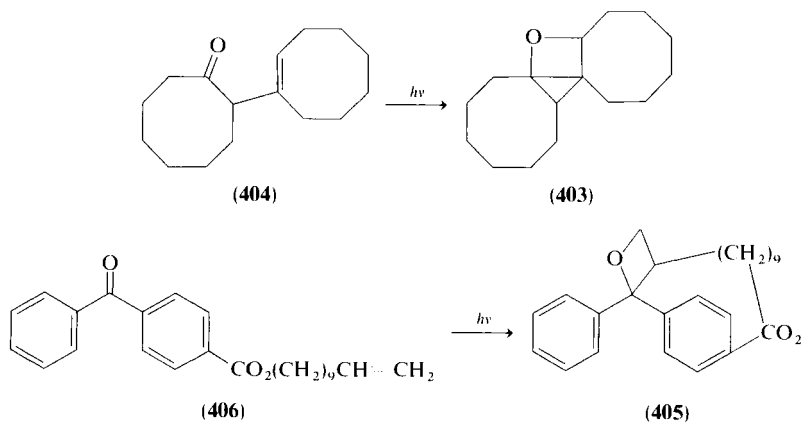
³⁵¹ J. C. Dalton and S. J. Tremont, *J. Am. Chem. Soc.* **97**, 6916 (1975).

³⁵² J. Mattay, *Tetrahedron Lett.*, 2309 (1980).



SCHEME 26

is relatively rare in other unsaturated ketones. An oxetan (**403**) is formed on irradiation of the β,γ -unsaturated ketone (**404**),³⁵³ and transannular oxetan formation readily occurs on irradiation of *trans*-cyclodec-5-enone.³⁵⁴ The oxetan-containing *p*-cyclophane (**405**) was obtained in high yield by irradiation of the substituted benzophenone (**406**).³⁵⁵



A systematic study of the photochemistry of thiones has been undertaken.³⁵⁶ Not surprisingly, cycloaddition to alkenes to give thietans is one pathway that commonly occurs. The reactions appear to be wavelength dependent, and stereospecific addition takes place via the S_2 excited state and nonstereospecific addition via the T_1 state. The photoaddition of

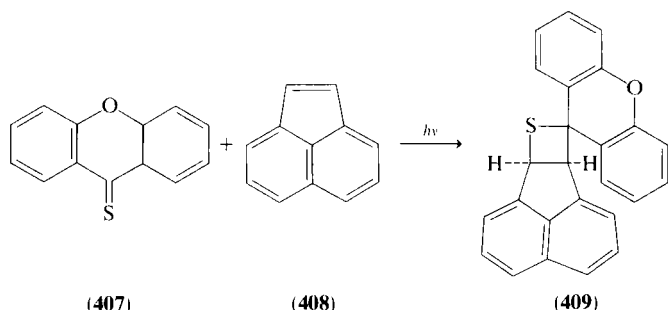
³⁵³ R. C. Cookson and N. R. Rogers, *J. C. S. Chem. Commun.*, 809 (1972).

³⁵⁴ G. L. Lange and M. Bosch, *Tetrahedron Lett.*, 315 (1971).

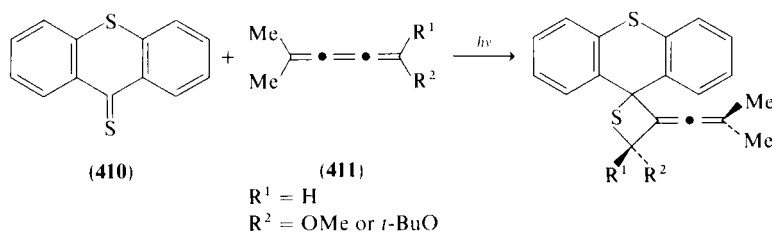
³⁵⁵ D. Bichan and M. Winnik, *Tetrahedron Lett.*, 3857 (1974).

³⁵⁶ P. de Mayo, *Acc. Chem. Res.* **9**, 52 (1976).

xanthione to electron-deficient alkenes, such as dimethyl maleate or dimethyl fumarate, takes place in this way,³⁵⁷ and there is evidence for biradical intermediates in the reaction of xanthione triplets with alkenes.³⁵⁸ Reaction takes place with a wide variety of alkenes; irradiation ($\lambda = 589$ nm) of xanthione (407) with acenaphthylene (408), for example, affords the thietan (409).³⁵⁹ Photocycloaddition of thioxanthione (410) to both the butatrienes



(411)³⁶⁰ and to alkyl-substituted pentatetraenes³⁶¹ yields spirothietans, as shown for the former in Scheme 27; 2-iminothietans are similarly prepared by photoaddition of thiones to ketenimines.³⁶²



SCHEME 27

Aliphatic and alicyclic thiones are less well investigated, principally because of their inherent instability. Adamantanethione, however, has been studied in detail and undergoes $[\pi 2 + \pi 2]$ cycloaddition to electron-deficient and electron-rich alkenes from both T_1 and S_2 excited states. Addition from the latter is more efficient than that from the triplet and is again stereospecific but not regiospecific. Addition of adamantanethione (412) to ethyl vinyl

³⁵⁷ H. Gotthardt, *Chem. Ber.* **105**, 2008 (1972).

³⁵⁸ N. J. Turro and V. Ramamurthy, *Tetrahedron Lett.*, 2423 (1976).

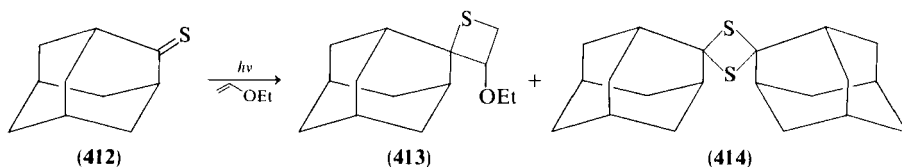
³⁵⁹ H. Gotthardt and S. Nieberl, *Chem. Ber.* **111**, 1471 (1978).

³⁶⁰ R. G. Visser and H. J. T. Bos, *Tetrahedron Lett.*, 4857 (1979).

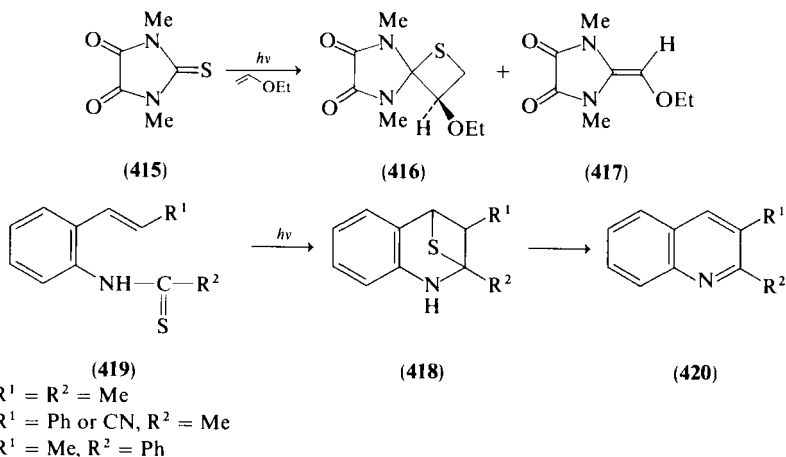
³⁶¹ R. G. Visser, E. A. Oostveen, and H. J. T. Bos, *Tetrahedron Lett.*, 1139 (1981).

³⁶² R. G. Visser, J. P. Baaji, A. C. Brouwer, and H. J. T. Bos, *Tetrahedron Lett.*, 4343 (1977).

ether on irradiation at $\lambda = 500$ nm proceeds via the triplet excited state and affords the thietan (413) and the dimer (414).³⁶³ Cycloaddition of di-*tert*-butylthione to various alkenes also takes place efficiently by way of the S_2



excited state,³⁶⁴ and addition of thioamides and thiolactams has been reported. Regiospecific addition, for example, has been observed on irradiation of the 2-thioparabanate (415) in the presence of ethyl vinyl ether to give the thietan (416) and alkene (417).³⁶⁵ Similar additions to indoline-2-thiones have been described,³⁶⁶ and this procedure has been employed in a new synthesis of desethylcatharanthine.³⁶⁷ Unstable thietans (418) have been detected as intermediates in the photochemically induced conversion of *o*-vinylthioanilides (419) to quinolines (420).³⁶⁸



³⁶³ A. H. Lawrence, C. C. Liao, P. de Mayo, and V. Ramamurthy, *J. Am. Chem. Soc.* **98**, 2219 (1976).

³⁶⁴ R. Rajee and V. Ramamurthy, *Tetrahedron Lett.*, 3463 (1978).

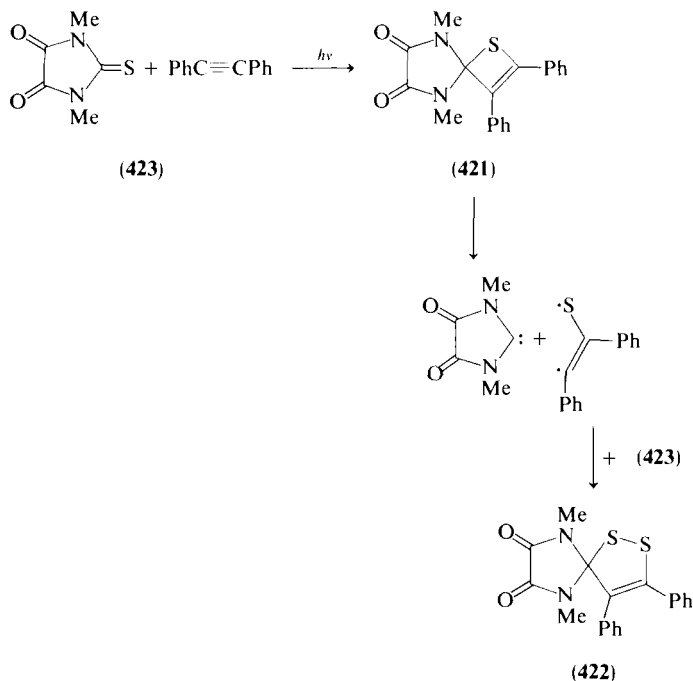
³⁶⁵ H. Gotthardt and S. Nieberl, *Chem. Ber.* **109**, 2871 (1976).

³⁶⁶ B. C. Das, J.-L. Fourrey, C. Marazano, A. Merrien, and J. Polonsky, *J. Chem. Res., Synop.*, 370 (1978).

³⁶⁷ C. Marazano, J.-L. Fourrey, and B. C. Das, *J. C. S. Chem. Commun.*, 37 (1981).

³⁶⁸ P. de Mayo, L. K. Sydnes, and G. Wenska, *J. Org. Chem.* **45**, 1549 (1980).

Thiets have been proposed as intermediates in the corresponding photo-addition of thiones to alkynes.³⁶⁹ The stable spirothiet (**421**) was obtained in this way along with the 1,2-dithiole (**422**) on irradiation of 1,3-dimethyl-2-thiobarabanic acid (**423**) with diphenylacetylene³⁷⁰; the proposed pathway is outlined in Scheme 28. Stable thiets have also been detected in the photo-addition of xanthenethione to bis(*tert*-butylthio)ethynes.³⁷¹



SCHEME 28

Oxets have similarly been proposed as intermediates in the photoaddition of carbonyl-containing compounds to alkynes.³⁷² The addition of the esters (**424**) to diphenylacetylene to give the α,β -unsaturated ketones (**425**) has been rationalized in this way.³⁷³ In contrast, no evidence was found for the

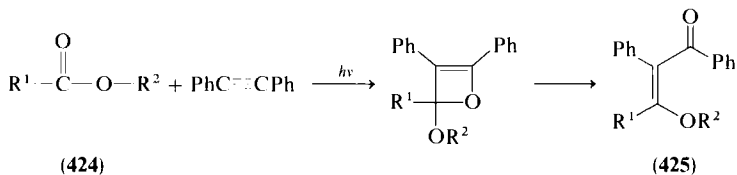
³⁶⁹ A. C. Brouwer and H. J. T. Bos, *Tetrahedron Lett.*, 209 (1976).

³⁷⁰ H. Gotthardt, S. Nieberl, and J. Donecke, *Justus Liebigs Ann. Chem.*, 873 (1980).

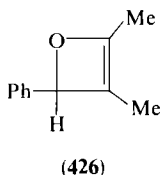
³⁷¹ A. C. Brouwer, A. V. E. George, D. Seykens, and H. J. T. Bos, *Tetrahedron Lett.*, 4839 (1978).

³⁷² H. J. T. Bos, H. T. van der Bend, J. S. M. Boleij, C. J. A. Everaars, and H. Polman, *Recl. Trav. Chim. Pays-Bas* **91**, 65 (1972); H. Polman, J. P. B. Baaij, and H. J. T. Bos, *ibid.* **98**, 176 (1979).

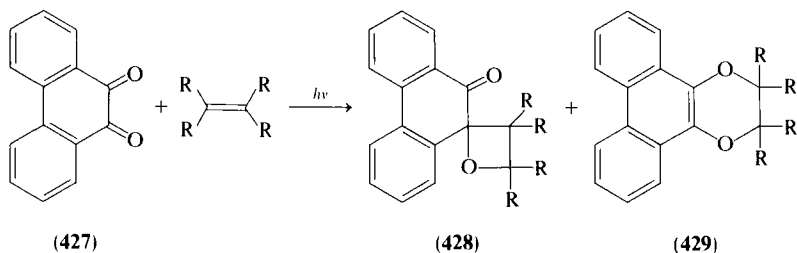
³⁷³ T. Miyamoto, Y. Shigemitsu, and Y. Odaira, *J. C. S. Chem. Commun.*, 1410 (1969).



intermediacy of an oxet in the reaction of benzaldehyde with hex-1-yne,³⁷⁴ whereas the oxet (426) was identified spectroscopically on irradiation of benzaldehyde and but-2-yne in dichloromethane at -78°C .³⁷⁵



$[\pi 2 + \pi 2]$ Cycloaddition competes with $[\pi 4 + \pi 2]$ cycloaddition on irradiation of phenanthroquinone (427) with alkenes to give the corresponding ketooxetans (428) and dihydrodioxins (429), as well as products arising by



hydrogen abstraction.³⁷⁶ The relative yields of the two adducts are dependent on the structure of the alkene; bicyclic alkenes, for example, have been shown to yield ketooxetans exclusively. Other *o*-quinones undergo the same photoaddition reaction,³⁷⁷ and phenanthroquinone affords analogous $[\pi 4 + \pi 2]$ photoadducts with alkenes.³⁷⁸ Photoaddition of α -diketones has also been observed,³⁷⁹ and irradiation of hexafluorobiacetyl in *cis*- or *trans*-difluoroethylene, for example, leads to the formation of the five adducts

³⁷⁴ J. S. Bradshaw, R. D. Knudsen, and W. W. Parish, *J. Org. Chem.* **40**, 529 (1975).

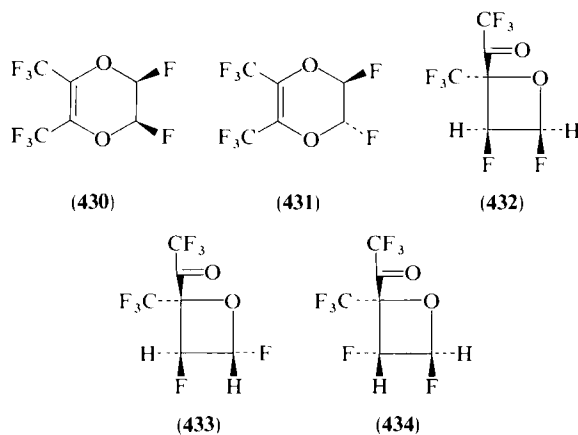
³⁷⁵ L. E. Friedrich and J. D. Bower, *J. Am. Chem. Soc.* **95**, 6869 (1973).

³⁷⁶ K. Maruyama, M. Muraoka, and Y. Naruta, *J. Org. Chem.* **46**, 983 (1981).

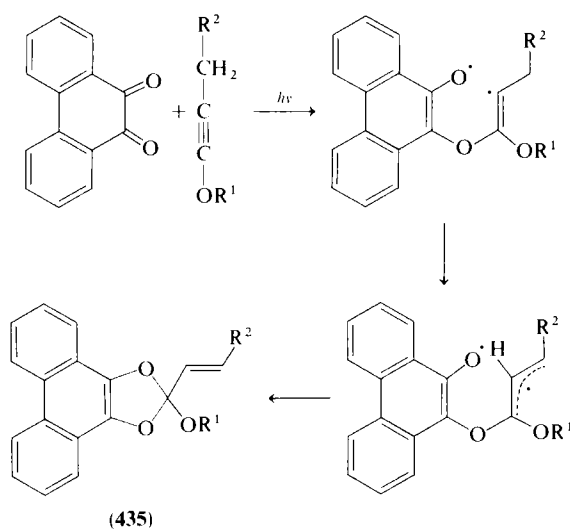
³⁷⁷ J. M. Bruce, in "The Chemistry of Quinonoid Compounds" (S. Patai, ed.), Part 1, p. 345. Wiley, New York, 1973.

³⁷⁸ J. S. M. Boleij and H. J. T. Bos, *Recl. Trav. Chim. Pays-Bas* **91**, 1212 (1972).

³⁷⁹ G. E. Gream, M. Mular, and J. C. Paice, *Tetrahedron Lett.*, 3479 (1970).



(430 to 434).³⁸⁰ Addition of phenanthroquinone to alkoxyalkynes, however, takes a different course and yields dioxoles **435**; the suggested mechanism is shown in Scheme 29.³⁸¹



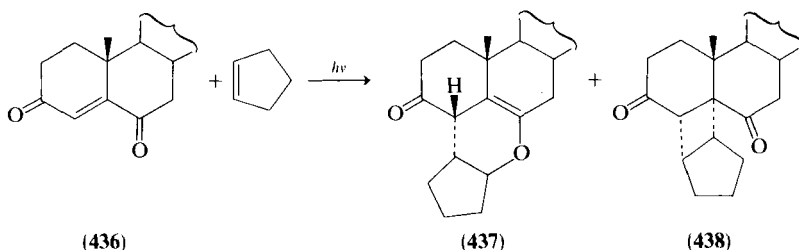
SCHEME 29

Competing $[\pi 4 + \pi 2]$ and $[\pi 2 + \pi 2]$ photoadditions of a different type have been reported in the steroidal enedione (**436**), which on irradiation in cyclopentene, is converted to the dihydropyran (**437**) and the cyclobutane (**438**).³⁸²

³⁸⁰ M. G. Barlow, B. Coles, and R. N. Haszeldine, *J. C. S. Perkin I*, 2523 (1980).

³⁸¹ H. J. T. Bos, H. Polman, and P. F. E. van Montfort, *J. C. S. Chem. Commun.*, 188 (1973).

³⁸² G. R. Lenz, *J. C. S. Chem. Commun.*, 700 (1977).



Examples of the formation of oxygen-containing heterocycles by processes involving $[6 + 2]^{383}$ and $[8 + 2]^{384}$ cycloadditions have also been described.

C. PHOTOADDITION TO HETEROCYCLES

A wide variety of photoadditions to unsaturated oxygen and sulfur heterocycles has been reported. It has, however, proved difficult to classify these processes, especially as the reaction mechanisms are not fully understood in all cases. Most additions of solvent to oxygen heterocycles arise via hydrogen abstraction pathways, often initiated by added ketone. Polar addition is relatively rare in these compounds; the addition of methanol to 6-methoxydifurocoumarone (439), however, does take place in this way to give adducts 440 to 442.³⁸⁵ Initial hydrogen abstraction is responsible for the photoaddition of propan-2-ol to the α,β -unsaturated lactones (443),³⁸⁶ the addition of methanol to chromenes,³⁸⁷ and the addition of hydrocarbon solvents to 2(5*H*)-furanone.³⁸⁸ Analogous additions of alcohols,³⁸⁹ ethers,³⁹⁰ and formamide³⁹¹ have been reported. The addition of formamide is normally acetone-initiated and arises via the $\cdot\text{CONH}_2$ radical; thus, irradiation of 2,3,4,6-tetra-*O*-acetyl-1-deoxy-D-arabino-hex-1-enopyranose (444) in

³⁸³ P. Courtot and R. Pichon, *J. C. S. Chem. Commun.*, 1103 (1972); N. C. Yang and W. Chiang, *J. Am. Chem. Soc.* **99**, 3163 (1977).

³⁸⁴ T. S. Cantrell, *J. Am. Chem. Soc.* **93**, 2540 (1971).

³⁸⁵ A. C. Weiss and M. Wiley, *J. C. S. Chem. Commun.*, 512 (1969).

³⁸⁶ K. Ohga and T. Matsuo, *J. Org. Chem.* **39**, 107 (1974).

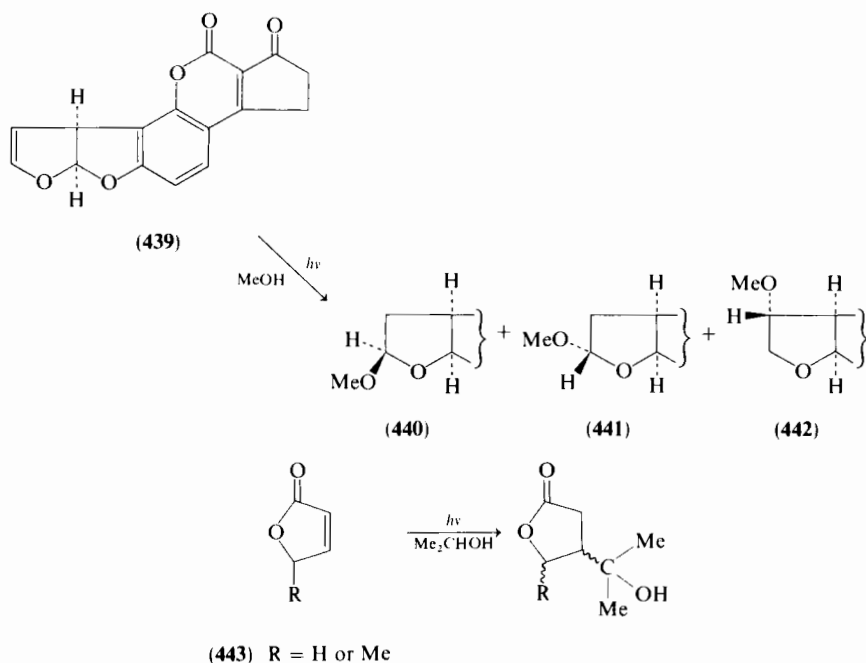
³⁸⁷ I. Yokoe, Y. Shirataki, and M. Komatsu, *Chem. Pharm. Bull.* **26**, 2277 (1978).

³⁸⁸ T. W. Flechter, *J. Org. Chem.* **42**, 901 (1977).

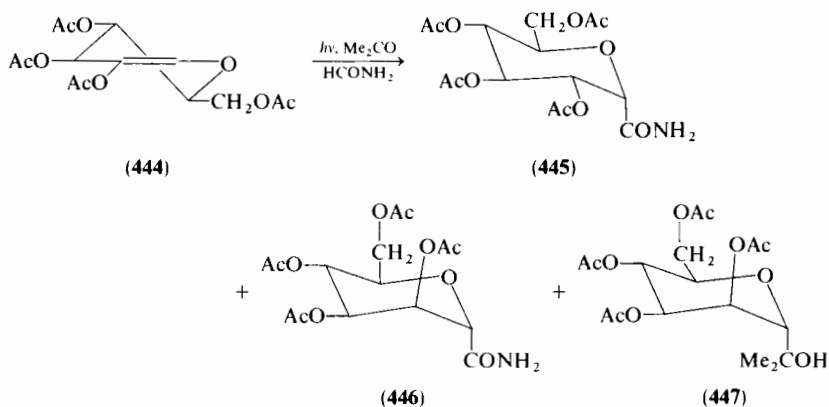
³⁸⁹ K. Matsuura, Y. Araki, Y. Ishido, and S. Satoh, *Chem. Lett.*, 849 (1972); Y. Araki, K. Nishiyama, K. Matsuura, and Y. Ishido, *Carbohydr. Res.* **63**, 288 (1978); D. L. Walker and B. Fraser-Reid, *J. Am. Chem. Soc.* **97**, 6251 (1975).

³⁹⁰ J. S. Jewell and W. A. Szarek, *Tetrahedron Lett.*, 43 (1969); K. Matsuura, K. Nishiyama, K. Yamada, and Y. Araki, *Bull. Chem. Soc. Jpn.* **46**, 2538 (1973); Y. Araki, K. Nishiyama, K. Senna, K. Matsuura, and Y. Ishido, *Carbohydr. Res.* **64**, 119 (1978).

³⁹¹ A. Rosenthal and K. Shudo, *J. Org. Chem.* **37**, 1608 (1972); A. Rosenthal and A. Zanlungo, *Can. J. Chem.* **50**, 1192 (1972); A. Rosenthal and M. Ratcliffe, *Carbohydr. Res.* **54**, 61 (1977).



acetone in the presence of formamide affords the amides (**445** and **446**) and the alcohol (**447**).³⁹²

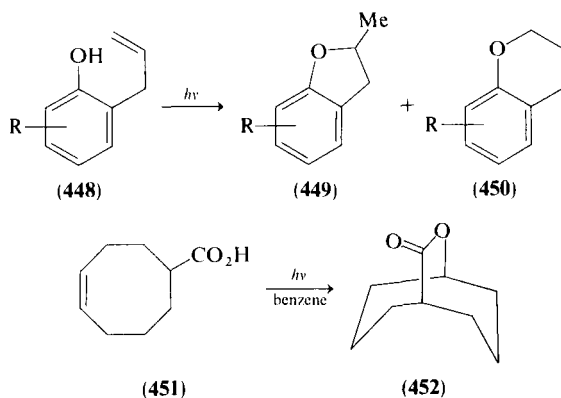


Intramolecular additions have been observed in the *o*-allylphenols (**448**), which on irradiation are converted to the cyclic ethers (**449** and **450**),³⁹³ and in cyclooctene carboxylic acid (**451**), which affords the lactone (**452**).³⁹⁴

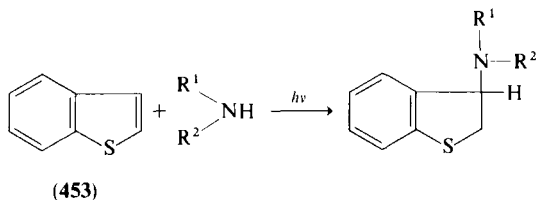
³⁹² A. Rosenthal and M. Ratcliffe, *Can. J. Chem.* **54**, 91 (1976).

³⁹³ S. Geresh, O. Levy, Y. Markovits, and A. Shani, *Tetrahedron* **31**, 2803 (1975).

³⁹⁴ H. Kato and M. Kawanisi, *Tetrahedron Lett.*, 865 (1970).



Additions of tetrahydrofuran to dimethylacetylenedicarboxylate³⁹⁵ and to tetracyanoethylene³⁹⁶ and of xanthene to 3,3-dimethyl-1,2-indanedione³⁹⁷ have also been described. Few systematic investigations of addition to sulfur heterocycles have been made and the topic merits further study. Primary and secondary amines, however, do undergo photoaddition to benzo[*b*]thiophene (453), as shown in Scheme 30.³⁹⁸



SCHEME 30

IV. Photocyclization

A. NORRISH TYPE II CYCLIZATIONS

Norrish Type II photocyclizations are the result of intramolecular hydrogen abstraction by an excited carbonyl group followed by cyclization of the resulting biradical. Hydrogen abstraction from the γ -carbon atom is preferred (1,5-hydrogen transfer). The introduction of a heteroatom into the

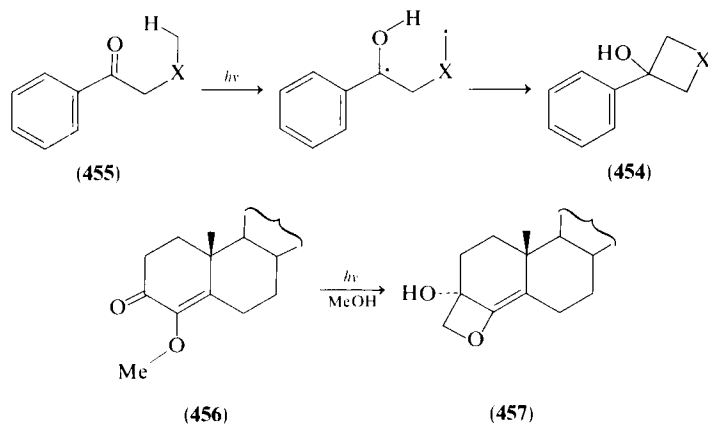
³⁹⁵ P. Singh, *J. Org. Chem.* **37**, 836 (1972).

³⁹⁶ M. Ohashi, S. Suwa, and Y. Osawa, *J. C. S. Chem. Commun.*, 884 (1977).

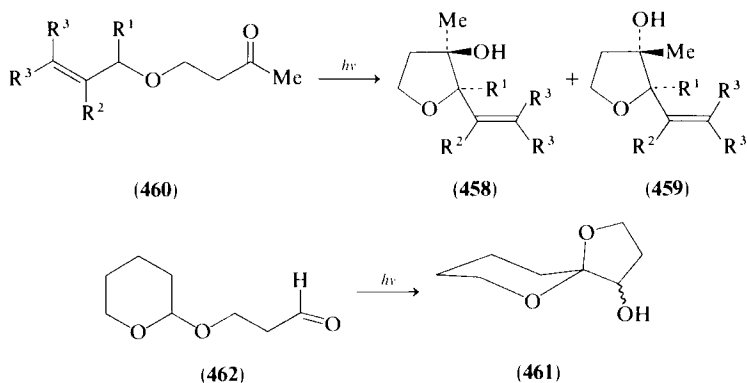
³⁹⁷ K. Maruyama, A. Osuka, and Y. Naruta, *Bull. Chem. Soc. Jpn.* **51**, 3047 (1978).

³⁹⁸ P. Grandclaudon, A. Lablache-Combier, and C. Párkányi, *Tetrahedron* **29**, 651 (1973).

alkyl chain thus provides a route to heterocycles. The oxetan (**454**: X = O) and the thietan (**454**: X = S) have been obtained in this way by irradiation of the ketones (**455**)³⁹⁹; other 3-hydroxyoxetans have been similarly prepared.⁴⁰⁰ Oxetans have also been obtained by photocyclization of 2-alkyloxycyclohex-2-enones.⁴⁰¹ 4-Methoxycholest-4-en-3-one (**456**) is similarly converted to the oxetan (**457**) in 50% yield,⁴⁰² and photocyclization has been observed in α -alkoxy- and α -dialkylaminomesityl oxides.⁴⁰³



Intramolecular δ -hydrogen abstraction (1,6-hydrogen transfer) is often a competing process and is preferred in the absence of a suitably positioned γ -hydrogen atom. 2-Alkenyl-3-hydroxytetrahydrofurans (**458**) and (**459**)



³⁹⁹ S. Majeti, *Tetrahedron Lett.*, 2523 (1971).

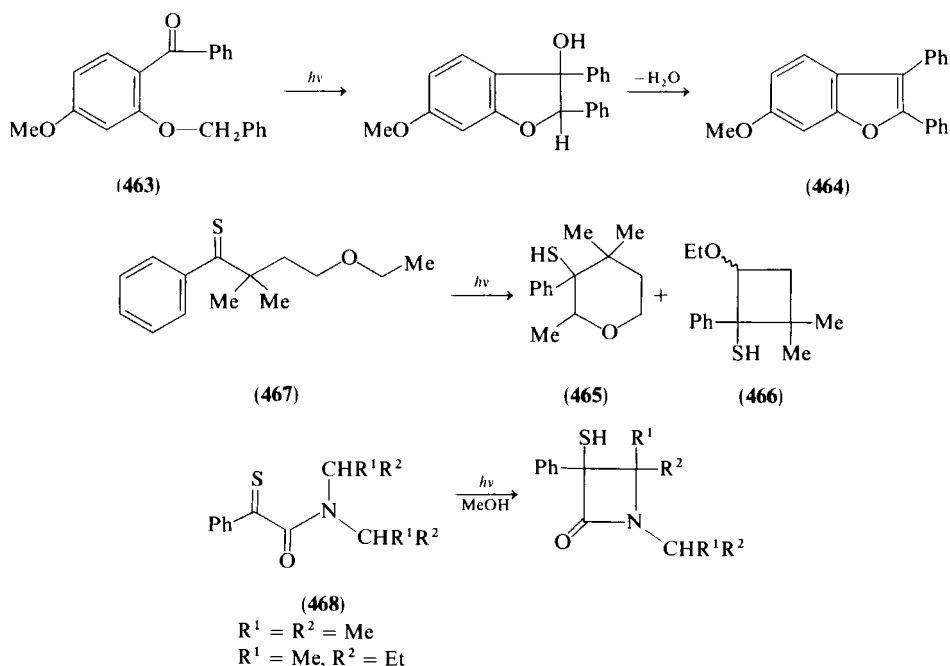
⁴⁰⁰ J. Kagan and J. T. Przybytek, *Tetrahedron* **29**, 1163 (1973).

⁴⁰¹ A. Enger, A. Feigenbaum, J.-P. Pete, and J.-L. Wolfhugel, *Tetrahedron* **34**, 1509 (1978).

⁴⁰² A. Feigenbaum and J.-P. Pete, *Bull. Soc. Chim. Fr.*, 351 (1977).

⁴⁰³ J. C. Arnould, A. Enger, A. Feigenbaum, and J.-P. Pete, *Tetrahedron* **35**, 2501 (1979).

have been synthesized in this way by irradiation of the β -allyloxy ketones (460)⁴⁰⁴ and the 1,6-dioxo[4.5]spirodecenes (461) have been similarly obtained from the aldehyde (462).⁴⁰⁵ The formation of tetrahydrofurans has been effected by photocyclizations of 4-methyl-4-alkoxy-pentan-2-ones⁴⁰⁶ and 3-oxobutylglycopyranosides,⁴⁰⁷ and 2-benzyloxy-4-methoxybenzophenone (463) is converted on irradiation to the benzo[*b*]furan (464).⁴⁰⁸ Analogous photocyclizations have been reported in *o*-benzyloxyphenylglyoxylates⁴⁰⁹ and in 2-allyloxyacetophenone.⁴¹⁰ Competing γ - and ϵ -hydrogen abstractions leading to the thiols (465 and 466) have been observed on irradiation of the thione (467).⁴¹¹ Aralkyl thiones on $\pi \rightarrow \pi^*$



⁴⁰⁴ H. A. J. Carless and D. J. Haywood, *J. C. S. Chem. Commun.*, 657 (1980).

⁴⁰⁵ T. Kožluk, L. Cottier, and G. Descotes, *Tetrahedron* **37**, 1875 (1981).

⁴⁰⁶ L. M. Stephenson and J. L. Parlett, *J. Org. Chem.* **36**, 1093 (1971).

⁴⁰⁷ G. Remy, L. Cottier, and G. Descotes, *Can. J. Chem.* **58**, 2660 (1980).

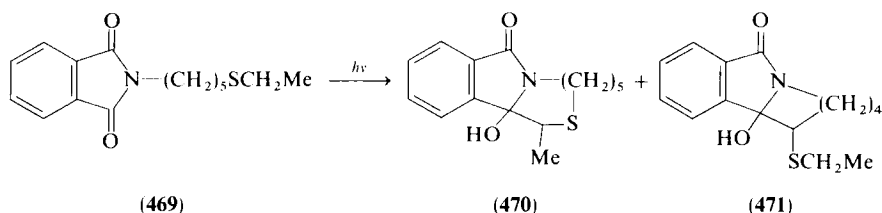
⁴⁰⁸ G. R. Lappin and J. S. Zannucci, *J. C. S. Chem. Commun.*, 1113 (1969); *J. Org. Chem.* **36**, 1808 (1971).

⁴⁰⁹ S. P. Pappas, J. E. Alexander, and R. D. Zehr, *J. Am. Chem. Soc.* **92**, 6927 (1970); S. P. Pappas and R. D. Zehr, *ibid.* **93**, 7112 (1971).

⁴¹⁰ F. Ryan and L. B. Jones, *J. C. S. Chem. Commun.*, 312 (1974).

⁴¹¹ S. Basu, A. Couture, K. W. Ho, M. Hoshino, P. de Mayo, and R. Suau, *Can. J. Chem.* **59**, 246 (1981).

excitation normally undergo intramolecular hydrogen abstraction from the δ -carbon atom yielding cyclopentanethiols, although an example of γ -hydrogen abstraction has been noted in α -phenylthioacetamides (**468**).⁴¹² A different mechanism, probably involving an electron-transfer step, is implicated in the "remote" photocyclization of sulfur-containing phthalimide derivatives to give medium- and large-ring azathiocyclols.⁴¹³ This is illustrated in Scheme 31 for the conversion of the phthalimide (**469**) to the thiazonine (**470**) and to the azepine (**471**) on irradiation in acetone; the reaction has been extended to include the formation of even larger rings.



SCHEME 31

B. NORRISH TYPE I RING EXPANSION REACTIONS

One of the pathways available to the biradicals arising by Norrish Type I homolysis in cyclic ketones is carbon-oxygen bond formation. The resulting oxacarbene undergoes dimerization or is trapped with an alcohol as the corresponding ether or with an alkene as a cyclopropane derivative. This reaction sequence is particularly favored in cyclobutanones and in other highly substituted cycloalkanones and results in the formation of oxygen heterocycles.⁴¹⁴ The cyclobutanone (**472**), for example, is converted in this way to the tetrahydrofuran (**473**) on irradiation in methanol.⁴¹⁵ Analogous ring expansions have been reported in other cyclobutanones⁴¹⁶ and in

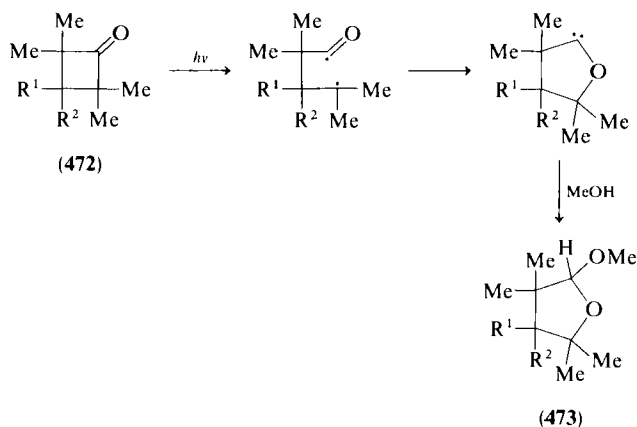
⁴¹² H. Aoyama, S. Suzuki, T. Hasegawa, and Y. Omote, *J. C. S. Chem. Commun.*, 899 (1979).

⁴¹³ Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka, and Y. Kanaoka, *J. Am. Chem. Soc.* **98**, 2349 (1976).

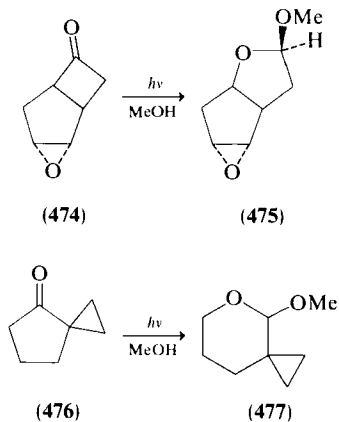
⁴¹⁴ N. J. Turro and D. R. Morton, *J. Am. Chem. Soc.* **93**, 2569 (1971).

⁴¹⁵ D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Am. Chem. Soc.* **92**, 4349 (1970).

⁴¹⁶ N. J. Turro, E. Lee-Ruff, D. R. Morton, and J. M. Conia, *Tetrahedron Lett.*, 2991 (1969); N. J. Turro, D. R. Morton, E. Hedaya, M. E. Kent, P. D'Angelo, and P. Schissel, *ibid.*, 2535 (1971); D. M. McDaniel and N. J. Turro, *ibid.*, 3035 (1972); K. Kimura, M. Takamura, S. Koshibe, M. Juro, Y. Fukuda, and Y. Odaira, *Bull. Chem. Soc. Jpn.* **49**, 741 (1976); N. M. Crossland, D. R. Kelly, S. M. Roberts, D. P. Reynolds, and R. F. Newton, *J. C. S. Chem. Commun.*, 681 (1979).



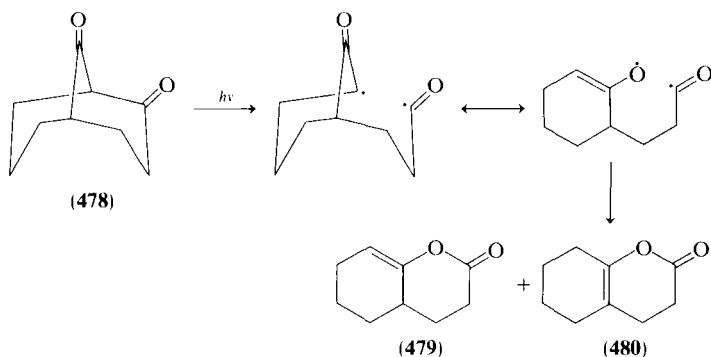
cyclobutane-1,2-diones.⁴¹⁷ Of particular note is the conversion of the fused cyclobutanone (474) into the tetrahydrofuran (475), a useful prostaglandin precursor.⁴¹⁸ Substituents capable of stabilizing oxacarbenes appear to promote ring expansion. Thus, the cyclopentanone (476) affords the tetrahydropyran (477) on irradiation in methanol.⁴¹⁹



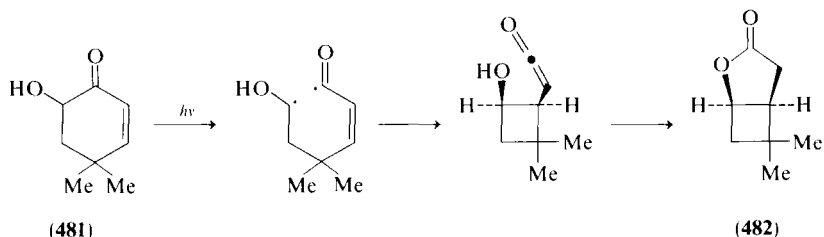
⁴¹⁷ O. L. Chapman, C. L. McIntosh, and L. L. Barber, *J. C. S. Chem. Commun.*, 1162 (1971); J. M. Denis and J. M. Conia, *Tetrahedron Lett.*, 461 (1973).

⁴¹⁸ R. F. Newton, D. P. Reynolds, N. M. Crossland, D. R. Kelly, and S. M. Roberts, *J. C. S. Perkin I*, 1583 (1980).

⁴¹⁹ J. K. Crandall and R. J. Seidewand, *J. Org. Chem.* **35**, 697 (1973); D. R. Morton and N. J. Turro, *J. Am. Chem. Soc.* **95**, 2836 (1973).



SCHEME 32



SCHEME 33

The photorearrangements of the 1,3-diketone (478) to the lactones (479 and 480)⁴²⁰ and of the 6-hydroxycyclohexenone (481) to the bicyclic lactone (482)⁴²¹ are also thought to involve α -cleavage; the proposed pathways are illustrated in Schemes 32 and 33, respectively.

Thiones, in general, do not undergo similar photoreactions. An exception to this behavior has been found in the thiolactone (483), which on irradiation in methanol is converted to the ether (484).⁴²² Photocyclization of a different type has been observed in the thione (485), leading to the formation of the thiophen (486).⁴²³ Details of the mechanism of this and related photocyclizations⁴²⁴ are not completely clear.

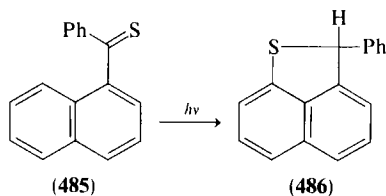
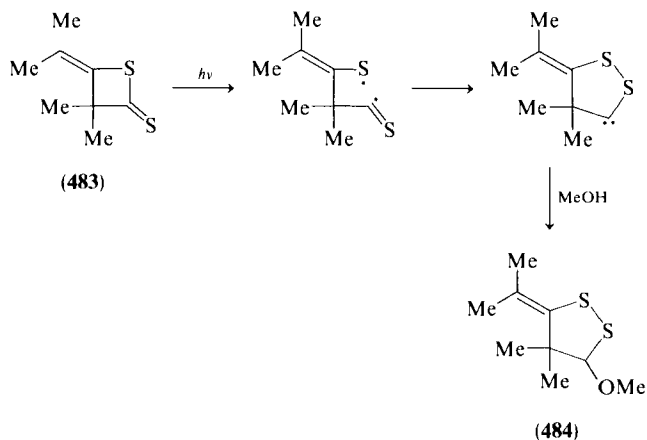
⁴²⁰ H. Kato, N. Miyamoto, M. Kawanisi, and H. Nozaki, *Tetrahedron* **26**, 2975 (1970).

⁴²¹ M. Jeffares and T. B. H. McMurray, *J. C. S. Chem. Commun.*, 793 (1976).

⁴²² J. Muthuramu and V. Ramamurthy, *J. Org. Chem.* **45**, 4532 (1980).

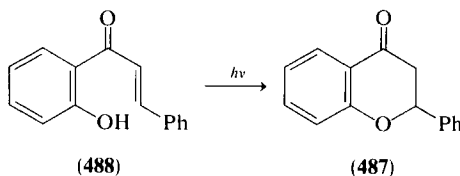
⁴²³ A. Cox, D. R. Kemp, R. Lapouyade, P. de Mayo, J. Jousot-Dubien, and R. Bonneau, *Can. J. Chem.* **53**, 2386 (1975).

⁴²⁴ A. de Leenheer, J. E. Sinsheimer, and J. H. Burckhalter, *J. Pharm. Sci.* **61**, 273 (1972).



C. MISCELLANEOUS PHOTOCYCLIZATIONS

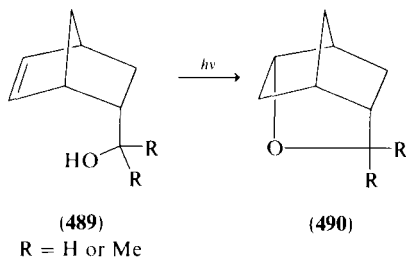
A wide range of other photocyclizations resulting in the formation of oxygen and sulfur heterocycles have been reported. Only those conversions that are generally applicable and that have some preparative value will be considered in this section. Flavanone (487) is obtained on irradiation of the 2'-hydroxychalcone (488)⁴²⁵; such transformations are best carried out in



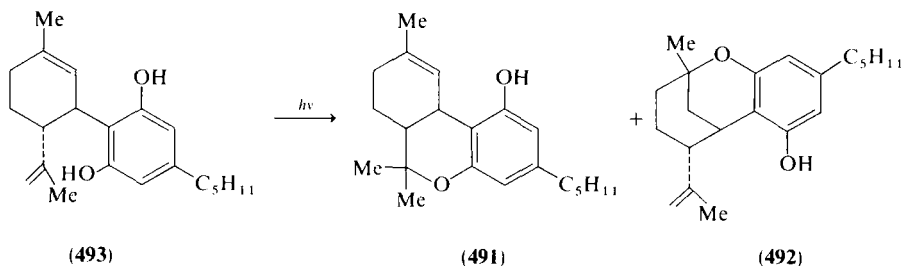
⁴²⁵ F. R. Sternmitz, J. A. Adamovics, and J. Geigert, *Tetrahedron* **31**, 1593 (1975).

ethyl acetate or dioxan.⁴²⁶ 2-Hydroxychalcones can themselves be prepared photochemically by Fries rearrangement of phenyl cinnamates.⁴²⁷

Photocyclization, arising by intramolecular hydroxyl addition to a carbon-carbon double bond, occurs in the norbornene derivatives (489) and yields the cyclic ethers (490).⁴²⁸ This is in marked contrast to the inter-



molecular photoreactions of norbornenes with alcohols, which proceed by way of radical pathways. An analogous photocyclization has been reported in a steroid derivative,⁴²⁹ and the cyclic ethers (491 and 492) are two of the products of irradiation of cannabidol (493) in cyclohexane.⁴³⁰



Cyclizations arising by intramolecular radical addition have been widely employed in the synthesis of oxygen and sulfur heterocycles. The tetrahydrofuran derivatives (494) have been prepared in this way via alkoxy radicals, generated in turn by photolysis of the unsaturated nitrites (495).⁴³¹ Bridged oxabicyclic compounds have been similarly prepared,⁴³² and the photodecomposition of a nitrite has been employed in the synthesis of the

⁴²⁶ R. Matsushima and I. Hirao, *Bull. Chem. Soc. Jpn.* **53**, 518 (1980).

⁴²⁷ V. T. Ramakrishnan and J. Kagan, *J. Org. Chem.* **35**, 2901 (1970).

⁴²⁸ P. J. Kropp and H. J. Krauss, *J. Am. Chem. Soc.* **91**, 7466 (1969).

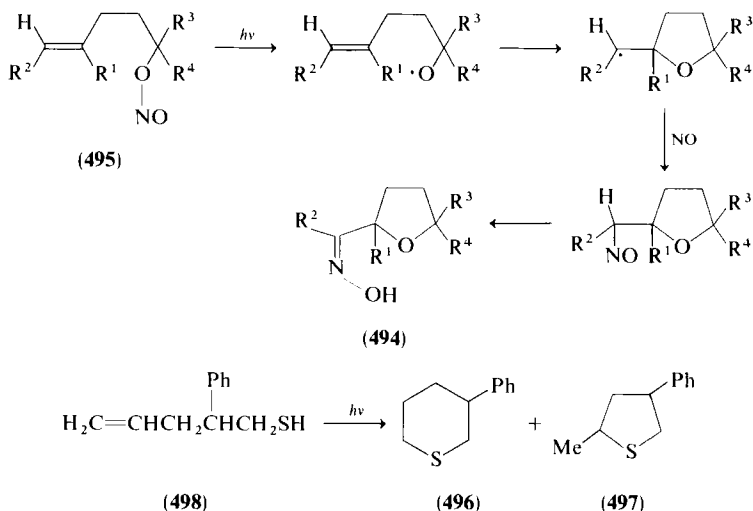
⁴²⁹ D. Guenard and R. Beugelmanns, *Tetrahedron* **32**, 781 (1976).

⁴³⁰ A. Shani and R. Mechoulam, *Tetrahedron* **27**, 601 (1971).

⁴³¹ M. P. Bertra and J. M. Surzur, *Bull. Soc. Chim. Fr.*, 2393 (1973).

⁴³² R. Nougier and J. M. Surzur, *Bull. Soc. Chim. Fr.*, 2399 (1973).

tetrahydropyran ring of (\pm)-tetrahydroanhydroaucubigenone.⁴³³ Thiyl radicals have proved useful in this context and can readily be prepared by photolysis of thiols⁴³⁴ and disulfides.⁴³⁵ The thian (496) and the thiole (497), for example, were obtained by irradiation of the thiol (498).⁴³⁶ Intramolecular addition of a photochemically generated thiyl radical to an alkyne has also been reported.⁴³⁷



D. PHOTOELIMINATION OF HX

Photocyclization arising by intramolecular elimination of HCl, HBr, or HI has been extensively used in the synthesis of nitrogen-containing heterocycles, but much less so in oxygen and sulfur systems. The mechanism of these transformations is not always clear: some proceed by way of an initial carbon-halogen bond homolysis, whereas others involve cyclization and

⁴³³ H. Obara, H. Kimura, M. Suzuki, and J. Onodera, *Bull. Chem. Soc. Jpn.* **51**, 3610 (1978).

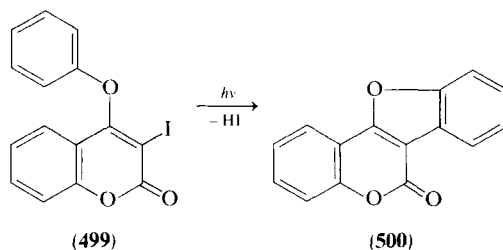
⁴³⁴ J.-M. Surzur, R. Nougier, M.-P. Crozet, and C. Dupuy, *Tetrahedron Lett.*, 2035 (1971); J.-M. Surzur, G. Bastien, M.-P. Crozet, and C. Dupuy, *C. R. Hebd. Seances Acad. Sci., Ser. C* **276**, 289 (1973); D. N. Jones, D. A. Lewton, J. D. Msonthi, and R. J. K. Taylor, *J. C. S. Perkin I*, 2637 (1974).

⁴³⁵ Y. Maki and M. Sako, *J. C. S. Chem. Commun.*, 836 (1978).

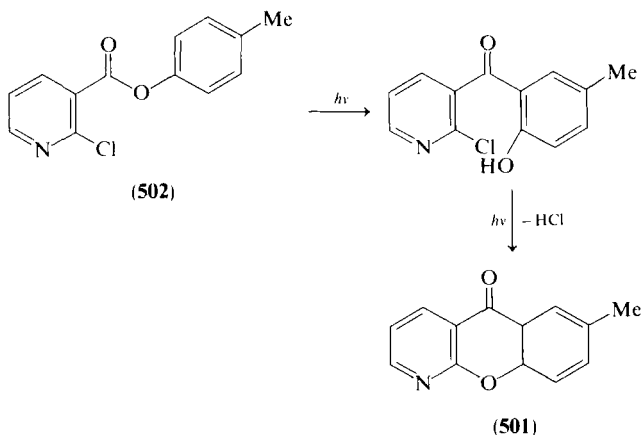
⁴³⁶ V. P. Krivonogov, V. I. Dronov, and N. K. Pokoneschikova, *Khim. Geterotsikl. Soedin.* **9**, 1204 (1975).

⁴³⁷ C. Dupuy, M. P. Crozet, and J.-M. Surzur, *Bull. Soc. Chim. Fr., Part 2*, 361 (1980).

subsequent elimination of HX. The ether (499), for example, was converted on irradiation to the tetracycle (500) with accompanying elimination of HI,⁴³⁸



and the 4-azaxanthone (501) was prepared from the nicotinate ester (502), as shown in Scheme 34.⁴³⁹ Similar photocyclizations have been observed in bromothiophen derivatives.⁴⁴⁰



SCHEME 34

Oxygen heterocycles have also been obtained on photolysis of hypoiodites.⁴⁴¹ Irradiation of the hypoiodite (503), for example, gave the tetrahydropyran (504) by the route shown in Scheme 35.⁴⁴²

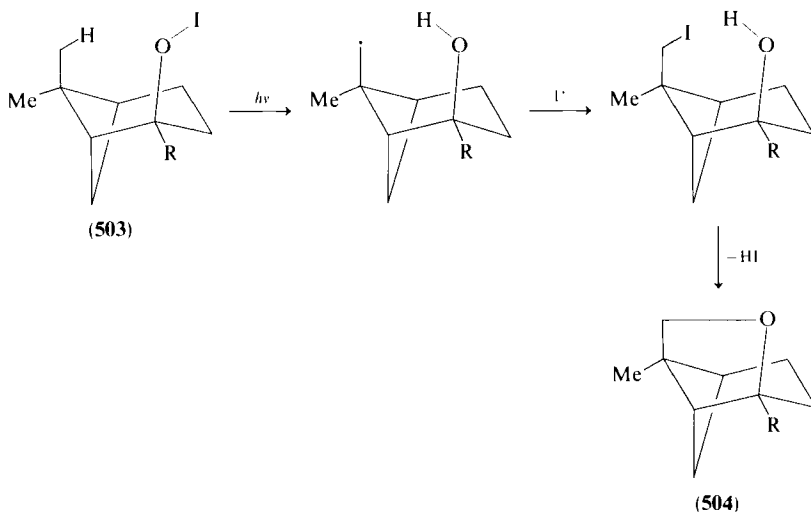
⁴³⁸ T. Kappe, G. Korbuly, and W. Stadlbauer, *Chem. Ber.* **111**, 3857 (1978).

⁴³⁹ K. Beelitz and K. Praefcke, *Justus Liebigs Ann. Chem.*, 1081 (1979).

⁴⁴⁰ See, for example, S. Jeganathan and M. Srinivasan, *Indian J. Chem., Sect. B* **19B**, 1028 (1980).

⁴⁴¹ H. Takahashi and M. Ito, *Chem. Lett.*, 373 (1979); H. Takahashi, M. Ito, H. Sugimoto, and T. Masamune, *ibid.*, 901.

⁴⁴² N. Bosworth and P. D. Magnus, *J. C. S. Perkin I*, 943 (1972).



SCHEME 35

V. Photoelimination

A. PHOTOELIMINATION OF CARBON DIOXIDE

Carboxylate esters readily undergo photodecomposition with loss of carbon dioxide. Not surprisingly, lactones and related oxygen heterocycles undergo related transformations. A wide variety of lactones behave in this fashion⁴⁴³; for example, the cyclic dilactone (505) is converted on irradiation to the [2.2]paracyclophane (506).⁴⁴⁴ Of particular interest is the use of the β -lactone (507) as a precursor of matrix-isolated cyclobutadiene (508).⁴⁴⁵

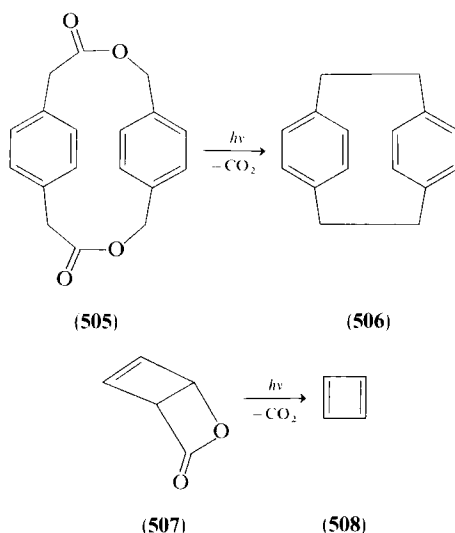
Phthaloyl peroxide (509) has similarly been employed as a precursor of benzyne (510).⁴⁴⁶ A careful examination in an argon matrix at 8 K has revealed that the β -lactone (511) and the keto ketene (512) are intermediates

⁴⁴³ R. S. Givens and W. F. Oettle, *J. Am. Chem. Soc.* **93**, 3301 (1971); *J. Org. Chem.* **37**, 4325 (1972); D. W. Jones and G. Kneen, *J. C. S. Perkin I*, 175 (1975).

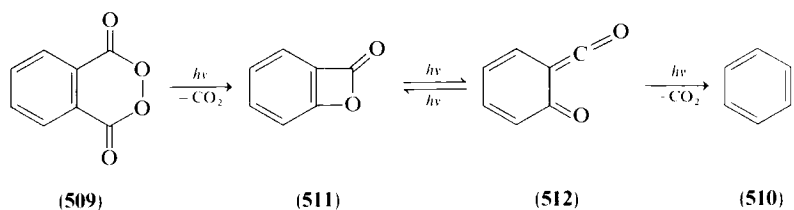
⁴⁴⁴ M. L. Kaplan and E. A. Truesdale, *Tetrahedron Lett.*, 3665 (1976).

⁴⁴⁵ O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.* **95**, 614 (1973); A. Krantz, C. Y. Lin, and M. D. Newton, *ibid.*, 2744; R. G. S. Pong, B.-S. Huang, J. Laureni, and A. Krantz, *ibid.* **99**, 4153 (1977).

⁴⁴⁶ M. Jones and M. R. De Camp, *J. Org. Chem.* **36**, 1536 (1971).



in this conversion, as shown in Scheme 36.⁴⁴⁷ Attempts to generate triplet benzyne by benzophenone-sensitized decomposition of phthaloyl peroxide give only products characteristic of singlet benzyne.⁴⁴⁸ Cyclohexene is formed in good yield on irradiation of *cis*- and *trans*-1,2-hexahydrophthaloyl peroxides,⁴⁴⁹ and the oxiran (**513**) is obtained on photodecomposition of the cyclic oxalate ester (**514**).⁴⁵⁰ Photoelimination of carbon dioxide from



SCHEME 36

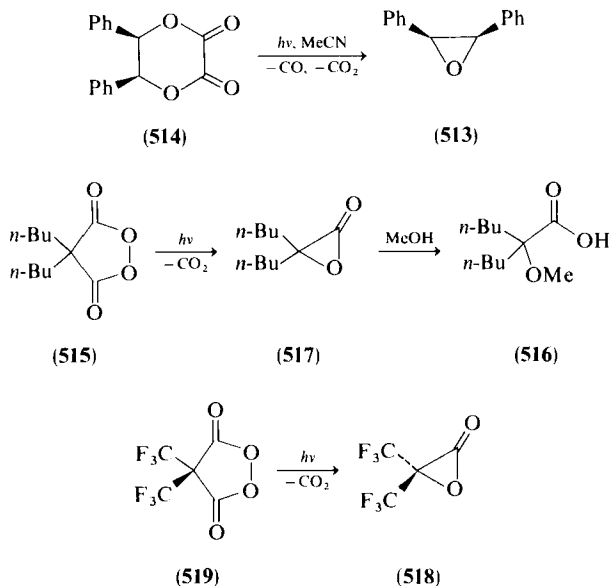
⁴⁴⁷ V. Dvorák, J. Kolc, and J. Michl, *Tetrahedron Lett.*, 3443 (1972); O. L. Chapman, K. Mattes, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.* **95**, 6134 (1973).

⁴⁴⁸ R. T. Luijbrand and R. W. Hoffmann, *J. Org. Chem.* **39**, 3887 (1974).

⁴⁴⁹ P. B. Dervan and C. R. Jones, *J. Org. Chem.* **44**, 2116 (1979).

⁴⁵⁰ R. C. White, *Tetrahedron Lett.*, 1021 (1980).

malonyl peroxides provides a route to highly reactive α -lactones.⁴⁵¹ The di-*n*-butyl derivative (515), for example, is converted to the acid (516) via the α -lactone (517) on irradiation in methanol. The stable α -lactone (518) has been prepared on a preparative scale by irradiation of the peroxide (519) at -15°C .⁴⁵²



Anhydrides also undergo photodecomposition with loss of carbon dioxide.⁴⁵³ Tetrafluorocyclobutadiene (520) can be prepared in this way from the anhydride (521) and is isolated as the $[\pi 4 + \pi 2]$ adduct (522) with furan.⁴⁵⁴ In the absence of furan, the dimer (523) and the cyclooctatetraene (524) were obtained. Examples of photoelimination of carbon dioxide from cyclic carbonates have been described.⁴⁵⁵

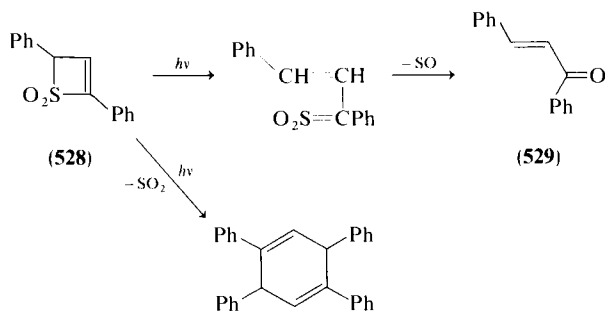
⁴⁵¹ O. L. Chapman, P. W. Wojkowski, W. Adam, O. Rodriguez, and R. Rucktäschel, *J. Am. Chem. Soc.* **94**, 1365 (1972); W. Adam and R. Rucktäschel, *J. Org. Chem.* **43**, 3886 (1978).

⁴⁵² W. Adam, J.-C. Liu, and O. Rodriguez, *J. Org. Chem.* **38**, 2269 (1973).

⁴⁵³ T. W. Fletcher, L. J. Szabo, and L. J. Koenig, *J. Org. Chem.* **41**, 2038 (1976); I. R. Dunkin and J. G. MacDonald, *J. C. S. Chem. Commun.*, 772 (1979); A. A. M. Roof, H. F. van Woerden, and H. Cerfontain, *J. C. S. Perkin II*, 838 (1980), and references therein.

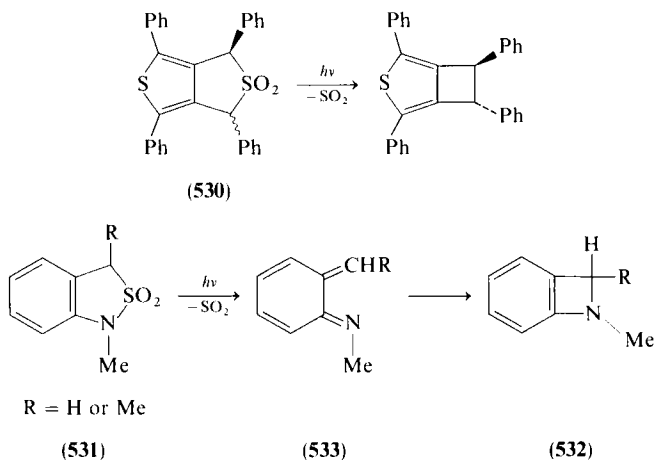
⁴⁵⁴ M. J. Gerace, D. M. Lemal, and H. Ertl, *J. Am. Chem. Soc.* **97**, 5584 (1975).

⁴⁵⁵ G. W. Griffin, R. L. Smith, and A. Manmade, *J. Org. Chem.* **41**, 338 (1976); E. A. Harrison and H. L. Ammon, *ibid.* **45**, 943 (1980).



SCHEME 37

phen 1,1-dioxides are converted to buta-1,3-diene derivatives.⁴⁵⁹ Photoelimination of sulfur dioxide, accompanied by ring contraction, has also been reported in 3,5-diphenyl-4*H*-thiopyran-4-one 1,1-dioxide,⁴⁶⁰ in the sultams (531), which yield the benzazetidines (532) via the quinonemethane imine intermediates (533),⁴⁶¹ and in the 1,2-dithiole 1,1-dioxide (534).⁴⁶²



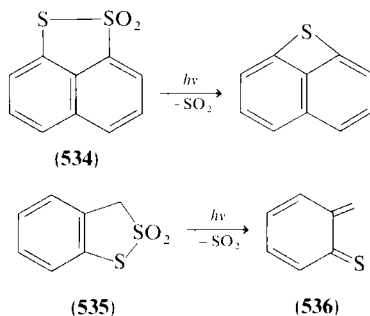
3*H*-1,2-Benzodithiole 2,2-dioxide (535), however, is converted on irradiation in benzene to the *o*-thiobenzoquinone methide (536), a species that is readily

⁴⁵⁹ W. L. Prins and R. M. Kellogg, *Tetrahedron Lett.*, 2833 (1973).

⁴⁶⁰ W. Ried and H. Bopp, *Angew. Chem., Int. Ed. Engl.* **16**, 653 (1977).

⁴⁶¹ M. Lancaster and D. J. H. Smith, *J. C. S. Chem. Commun.*, 471 (1980).

⁴⁶² J. Meinwald and S. Knapp, *J. Am. Chem. Soc.* **96**, 6532 (1974).



trapped as the adduct of *N*-phenylmaleimide.⁴⁶³ Photofragmentation accompanied by loss of sulfur dioxide has been observed in 1,2,3-thiadiazole 1,1,2-trioxides⁴⁶⁴ and in 1,2,3-thiadiazole 1,1,3-trioxides⁴⁶⁵; cyclopropane derivatives have been obtained by photoelimination of sulfur dioxide from γ -sultines.⁴⁶⁶ In a related process, vinylene trithiocarbonates are converted on irradiation in an argon matrix to thiirens by loss of carbon disulfide.⁴⁶⁷

C. PHOTOELIMINATION OF NITROGEN

The photoelimination of nitrogen from azo compounds, diazo compounds, and azides is a topic that has been thoroughly reviewed elsewhere. These transformations are found in oxygen and sulfur heterocycles, but as they are not unique to these systems, they will not be discussed in this article. Examples can be found in a review on the photochemistry of nitrogen-containing heterocycles.¹

⁴⁶³ A. G. Hortmann, A. J. Aron, and A. K. Bhattacharya, *J. Org. Chem.* **43**, 3374 (1978).

⁴⁶⁴ G. Trickes, U. Pleucken, and H. Meier, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **32B**, 956 (1977).

⁴⁶⁵ G. Trickes, H. P. Braun, and H. Meier, *Justus Liebigs Ann. Chem.*, 1347 (1977).

⁴⁶⁶ T. Durst, J. C. Huang, N. K. Sharma, and D. J. H. Smith, *Can. J. Chem.* **56**, 512 (1978).

⁴⁶⁷ M. Torres, A. Clement, H. E. Gunning, and O. P. Strausz, *Nouv. J. Chim.* **3**, 149 (1979).

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Reactivity of Naphthyridines toward Nitrogen Nucleophiles

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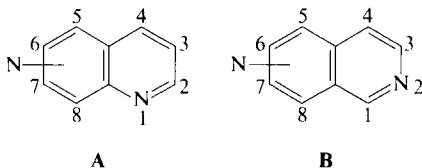
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I. Introduction

Naphthyridines are heterocyclic systems consisting of two fused aromatic rings, each one containing one nitrogen atom. Two groups of naphthyridines can be discerned: the 1,X-naphthyridines (X = 5, 6, 7, and 8; see **A**) and the 2,X-naphthyridines (X = 6 and 7; see **B**). Both groups are π -electron deficient and therefore highly susceptible to nucleophilic attack and strongly deactivated for electrophilic attack.



It is not surprising that the behavior of naphthyridines toward nucleophiles has been a subject of numerous studies¹⁻⁸ and that nucleophilic substitution in naphthyridines has become a very valuable and efficient method to synthesize substituted naphthyridines. In the last decade many important and new features of nucleophilic substitution in naphthyridines using nitrogen nucleophiles (especially liquid ammonia and potassium amide/liquid ammonia) have been found. In view of these recent results it seems worthwhile to review this area of research. The present chapter is concerned with the reactions of naphthyridine with nitrogen nucleophiles; for a full review of naphthyridine chemistry, see the chapter by Paudler and Sheets, p. 147 of this volume.

This review is outlined as follows: first, the pattern of addition occurring between naphthyridines or substituted naphthyridines and azanucleophiles is discussed; second, attention will be paid to nucleophilic substitutions using nitrogen nucleophiles such as amide ions and liquid ammonia; and third,

¹ C. F. Allen, *Chem. Rev.* **47**, 275 (1950).

² M. J. Weiss and C. R. Hauser, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), **7**, 198. Wiley Interscience, New York, 1961.

³ R. G. Shepherd and J. L. Fredrick, *Adv. Heterocycl. Chem.* **4**, 141 (1965).

⁴ W. W. Paudler and T. J. Kress, in "Topics in Heterocyclic Chemistry" (R. N. Castle, ed.), Chapter 4. Wiley (Interscience), New York, 1969; *Adv. Heterocycl. Chem.* **11**, 123 (1970).

⁵ Y. Hamada and I. Takeuchi, *Yuki Gosei Kagaku Kyokaishi* **32**, 602 (1974).

⁶ W. Czuba, *Khim. Geterotsikl. Soedin.*, **3** (1979).

⁷ W. Czuba, *Wiad. Chem.* **34**, 263 (1980); **35**, 441 (1981).

^{7a} M. Woźniak, *Wiad. Chem.* **32**, 283 (1978).

⁸ M. Woźniak and H. C. van der Plas, *Heterocycles* **19**, 363 (1982).

ring transformations are discussed, which naphthyridines can undergo in reactions with the above-mentioned nucleophiles.

II. Covalent Amination

The first paper on the addition of water to the C=N bond in naphthyridines (covalent hydration) appeared in 1963,⁹ but it was not until 1976 that the first report concerning covalent amination of naphthyridines using potassium amide in liquid ammonia was published.¹⁰

In covalent amination the amino group adds to the annular carbon atom either ortho or para to the ring nitrogen. The amino group is covalently (σ) bonded to the carbon; depending on the strength of the base used, the σ -adduct is either neutral or present in its anionic form. In this review the adducts are called aminodihydronaphthyridines when the species are neutral and aminodihydronaphthyridinides when the species are present in their anionic forms.

Extensive studies have shown that covalent amination is a more general phenomenon than covalent hydration; systems that are not able to undergo covalent hydration may easily undergo covalent amination. The 1,X- and 2,X-naphthyridines illustrate this phenomenon clearly. Whereas all parent naphthyridines do not give covalent σ -adducts with water (in basic as well as in acidic mediums), addition of the amide ions easily takes place using potassium amide in liquid ammonia, and the corresponding σ -adducts easily formed.

A useful tool to detect the occurrence of covalent amination in liquid ammonia and to assign the structures of the σ -adducts is ¹H- and ¹³C-NMR spectroscopy. On addition of the nitrogen nucleophile to the sp^2 carbon atom of the aromatic heterocycle, this atom changes its hybridization from sp^2 to sp^3 , which is reflected in a considerable upfield shift of that particular carbon atom and the hydrogen atom attached to it.

Complex ¹H-NMR spectra of σ -adducts can often be simplified by use of specifically deuterium-labeled compounds. By comparison of the undeuterated with the deuterated covalent amino σ -adducts, in many cases the ¹H-NMR peaks can be easily assigned.

The upfield shifts that are usually observed for the carbon atom that rehybridizes lie between 83 and 88 ppm; for the hydrogen attached to that carbon, upfield shifts between 3.9 and 4.3 ppm are found. In addition, adduct formation also leads to a change of the J_{13C-H} coupling constant from about 180 Hz (sp^2) to about 150 Hz at the tetrahedral center. Sometimes the signal of the hydrogen attached to the sp^3 carbon atom carrying the amino group

⁹ A. Albert and W. L. F. Armarego, *J. Chem. Soc.*, 4237 (1963).

¹⁰ H. C. van der Plas, M. Woźniak, and B. van Veldhuizen, *Tetrahedron Lett.*, 2087 (1976).

TABLE I
REACTIVITY INDICES FOR THE NUCLEOPHILIC REACTIONS
OF THE NAPHTHYRIDINES

Compound	Position	q_r^a			S_r^{-e}	f_r^{-f}
		HMO ^b	HMO ^c	PPP ^d		
1,5-Naphthyridine (1)	2,6	0.899	0.79	0.846	1.178	0.203
	3,7	0.993	0.99	1.020	0.953	0.116
	4,8	0.945	0.89	0.951	1.293	0.360
1,6-Naphthyridine (4)	2	0.881	0.77	0.803	1.228	0.285
	3	1.009	1.02	1.057	0.887	0.079
	4	0.917	0.83	0.933	1.338	0.446
	5	0.885	0.77	0.829	1.339	0.398
	7	0.930	0.86	0.870	1.003	0.070
1,7-Naphthyridine (7)	8	1.021	1.04	1.040	1.045	0.264
	2	0.895	0.78	0.850	1.173	0.208
	3	0.993	0.98	1.008	0.953	0.133
	4	0.935	0.86	0.965	1.291	0.394
	5	0.997	0.99	1.035	1.115	0.286
1,8-Naphthyridine (11)	6	0.949	0.89	0.903	0.950	0.323
	8	0.909	0.81	0.832	1.296	0.369
	2,7	0.883	0.78	0.817	1.235	0.251
	3,6	1.011	1.02	1.052	0.884	0.078
	4,5	0.922	0.85	0.947	1.342	0.392
2,6-Naphthyridine (13)	1,5	0.898	0.79	—	—	—
	3,7	0.946	0.89	—	—	—
	4,8	0.993	0.99	—	—	—
2,7-Naphthyridine (15)	1,8	0.880	0.75	—	—	—
	3,6	0.930	0.86	—	—	—
	4,5	1.012	1.02	—	—	—

^a q_r = π -electron density.

^b Hückel molecular orbital calculations, $h_N = 0.5$.^{13,14,18}

^c Hückel molecular orbital calculations, $h_N = 1.1$.¹⁹

^d Pariser-Parr-Pople molecular orbital calculations.¹⁴

^e S_r^{-} = superdelocalizability.^{13,14}

^f f_r^{-} = frontier electron density.^{13,14}

is split due to coupling with the geminal amino group. However, the coupling is found to be dependent on the potassium amide concentration: at a greater concentration no coupling is observed because the hydrogens of the amino group easily undergo a rapid amide-induced exchange.^{11,12}

On the basis of HMO calculations, which also take into account the nature of the nucleophilic reagents, it has been found that from the various

¹¹ J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King, and P. E. Kandetzki, *J. Org. Chem.* **38**, 1947 (1973).

¹² J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.* **94**, 682 (1972).

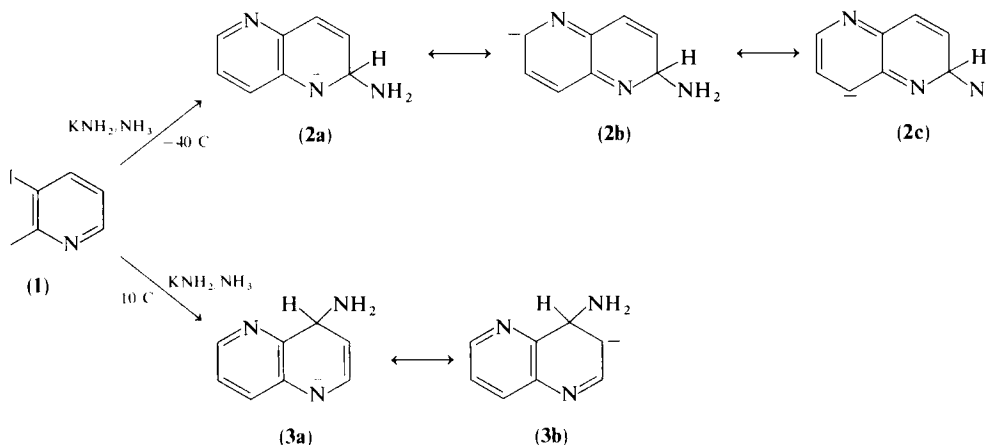
reactivity indices for nucleophilic attack (i.e., electron density $[q_r]$, superdelocalizability $[S_r^-]$, and frontier orbital electron density $[f_r^-]$), the electron density is the most suitable parameter for predicting the orientation of the addition of the amide ion or ammonia (Table I).^{13,14} The addition reaction to the parent naphthyridines is found to be very fast,^{15,16} which means that in the transition state for addition the electron distribution is close to that in the starting material.¹⁷

In the following section we discuss the σ -adduct formation between 1,X- and 2,X-naphthyridines using potassium amide in liquid ammonia and the influence of the temperature on the addition pattern.

A. COVALENT AMINATION OF THE PARENT NAPHTHYRIDINES

1. 1,5-Naphthyridine

On dissolving the title compound (1) in KNH_2/NH_3 the ^1H - and ^{13}C -NMR spectra of that solution indicated the presence of 2-aminodihydro-1,5-naphthyridinide (2); no trace of compound 1 could be detected.^{15,16}



¹³ M. Hirota, H. Masuda, Y. Hamada, and I. Takeuchi, *Bull. Chem. Soc. Jpn.* **52**, 1498 (1979).

¹⁴ M. Hirota, K. Abe, H. Endo, and H. Masuda, *Kenkyu Hokoku--Asahi Garasu Kogyo Gijutsu Shoreikai* **35**, 109 (1979).

¹⁵ H. C. van der Plas, B. van Veldhuizen, M. Woźniak, and P. Smit, *J. Org. Chem.* **43**, 1673 (1978).

¹⁶ H. J. W. van den Haak, H. C. van der Plas, and B. van Veldhuizen, *J. Org. Chem.* **46**, 2134 (1981).

¹⁷ For the study on the formation of σ adducts between parent azines or their derivatives, and potassium amide in liquid ammonia, we refer to reference 21 and the literature cited therein.

In the spectrum of σ -adduct **2** the absorptions of all carbons and hydrogens were shifted upfield, compared to the chemical shifts of the corresponding atoms in **1** (Tables II and III). The most pronounced upfield shifts are those of H-2 ($\Delta\delta = 3.99$ ppm) and of C-2 ($\Delta\delta = 85.2$ ppm). In accordance with the formation of **2** is the change in the magnitude of $J_{C(2)-H}$ (180 Hz in **1** and 150 Hz in **2**). The results given in Table II also show that after C-2, C-6 is shifted upfield by the next largest amount ($\Delta\delta = 25.9$ ppm), reflecting a notable contribution of the para-para quinoid structure (**2b**).³ Also the presence of a negative charge on C-8 ($\Delta\delta = 15.6$ ppm; Table III), although less than on C-6 ($\Delta\delta = 25.9$ ppm; Table III), indicates that the ortho-para quinoid structure (**2c**) contributes to resonance stabilization of **2**.

It has been discussed that the addition of the amide ion is charge-controlled;^{13,16} this is in agreement with the fact that addition of the amide ion at -40°C takes place at C-2, which has the lowest electron density (see Table I). Interestingly, on heating of a solution of **2** in KNH_2/NH_3 from -40°C to $+10^\circ\text{C}$ the ^1H -NMR spectrum of the solution completely changed.¹⁶ The doublet at 4.97 ppm of H-2 in **2** and the quartet at 5.38 ppm of H-3 in **2** disappeared and a new doublet at 4.59 ppm and a new quartet at 4.18 ppm appeared (see Table II).

Analysis of the spectrum indicated that we are dealing here with the spectrum of 4-aminodihydro-1,5-naphthyridinide (**3**). The results obtained by ^{13}C -NMR spectroscopy support the formation of **3** (see Table III). From these data it is evident that the covalent amination of **1** by the amide anion is subjected to a kinetic and thermodynamic control. At low temperature (-40°C) the kinetically favored σ -adduct (**2**) is formed, and at higher temperature (10°C) the thermodynamically favored one (**3**) is formed.

The reason why σ -adduct **3** is more stable than **2** has been explained by the important contribution of azaallylic resonance (**3b**), which leads to a partial negative charge on C-3 and leaves one ring fully aromatic.¹⁶ This explanation is confirmed by the upfield shift value for C-3 in **3**. A similar resonance stabilization has been proposed in the σ -adduct 4-aminodihydroquinolinide.¹¹

2. 1,6-Naphthyridine

Hückel calculations have shown that in **4** positions 2 and 5 have lower electron densities than remaining positions 3, 4, 7, and 8.^{13,14,18,19} PPP calculations indicate, however, that position 2 has the lowest electron

¹⁸ S. C. Wait, Jr. and J. W. Wesley, *J. Mol. Spectrosc.* **19**, 25 (1966).

¹⁹ W. W. Paudler and T. J. Kress, *J. Org. Chem.* **33**, 1384 (1968).

TABLE II
¹H-NMR DATA OF PARENT NAPHTHYRIDINES AND THEIR 1:1 σ -ADDUCTS WITH AMIDE IONS

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8
1,5-Naphthyridine (1)	CDCl ₃	—	8.96	7.55	8.37	—	8.96	7.55	8.37
2-Aminodihydro-1,5-naphthyridinide (2)	KNH ₂ /NH ₃	—	4.97	5.38	^a	—	6.80	^a	^a
	$\Delta\delta$	—	3.99	2.17	—	—	2.16	—	—
4-Aminodihydro-1,5-naphthyridinide (3)	KNH ₂ /NH ₃	—	^a	4.18	4.59	—	7.31	^a	^a
	$\Delta\delta$	—	—	3.37	3.78	—	1.65	—	—
1,6-Naphthyridine (4)	CDCl ₃	—	9.03	7.43	8.20	9.22	—	8.75	7.87
2-Aminodihydro-1,6-naphthyridinide (5)	KNH ₂ /NH ₃	—	5.05	5.19	6.23	7.15	—	7.20	5.82
	$\Delta\delta$	—	3.98	2.24	1.97	2.07	—	1.55	2.05
1,7-Naphthyridine (7)	CDCl ₃	—	9.01	7.48	8.14	7.64	8.60	—	9.50
2-Aminodihydro-1,7-naphthyridinide (8)	KNH ₂ /NH ₃	—	5.02	5.31	6.28	6.35	6.76	—	7.52
	$\Delta\delta$	—	3.99	2.17	1.86	1.29	1.84	—	1.98
8-Aminodihydro-1,7-naphthyridinide (9)	KNH ₂ /NH ₃	—	7.65 ^b	6.77 ^b	6.77 ^b	4.52	7.01	—	5.13
	$\Delta\delta$	—	1.46	0.71	1.37	3.12	1.59	—	4.37
1,8-Naphthyridine (11)	CDCl ₃	—	9.15	7.51	8.21	8.21	7.51	9.15	—
2-Aminodihydro-1,8-naphthyridinide (12)	KNH ₂ /NH ₃	—	5.21	5.42	6.32	6.65	5.62	7.60	—
	$\Delta\delta$	—	3.94	2.09	1.89	1.56	1.89	1.55	—
2,6-Naphthyridine (13)	CDCl ₃	9.27	—	8.65	7.69	9.27	—	8.65	7.69
1-Aminodihydro-2,6-naphthyridinide (14)	KNH ₂ /NH ₃	5.03	—	7.09	4.70	7.78	—	7.64	6.84
	$\Delta\delta$	4.24	—	1.56	2.99	1.49	—	1.01	0.85
2,7-Naphthyridine (15)	CDCl ₃	9.37	—	8.68	7.59	7.59	8.68	—	9.37
1-Aminodihydro-2,7-naphthyridinide (16)	KNH ₂ /NH ₃	5.03	—	7.16	4.59	6.28	7.63	—	7.67
	$\Delta\delta$	4.34	—	1.52	3.00	1.31	1.05	—	1.70

^a These signals were detected as a multiplet at 6.20–6.50 ppm.

^b These signals show deceptive simplicity.

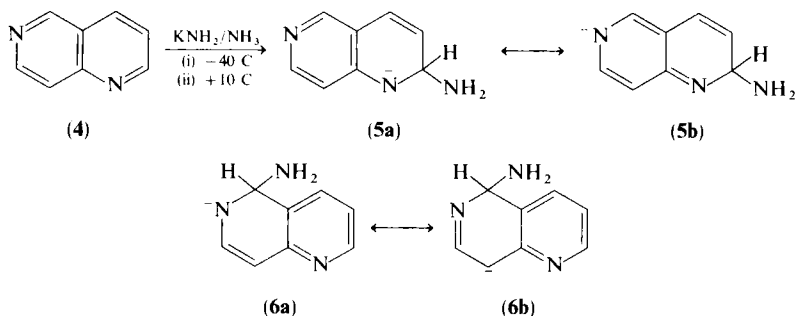
TABLE III
¹³C-NMR DATA OF PARENT NAPHTHYRIDINES AND THEIR 1:1 σ -ADDUCTS WITH AMIDE IONS

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1,5-Naphthyridine (1)	CDCl ₃	—	151.0	124.1	137.2	—	151.0	124.1	137.2	144.0	144.0
2-Aminodihydro-1,5-naphthyridinide (2)	KNH ₂ /NH ₃	—	65.8	121.3	127.4 ^a	—	125.1	122.1	121.6 ^a	151.2	137.3
	$\Delta\delta$	—	85.2	2.8	9.8	—	25.9	1.4	15.6	-7.2	6.7
4-Aminodihydro-1,5-naphthyridinide (3)	KNH ₂ /NH ₃	—	141.8	92.2	50.9	—	134.6	121.2	125.1	145.8 ^a	145.3 ^a
	$\Delta\delta$	—	9.2	31.9	86.3	—	16.4	2.9	12.1	-1.8	-1.3
1,6-Naphthyridine (4)	CDCl ₃	—	154.9	122.7	135.8	153.0	—	146.9	122.2	150.5	123.8
2-Aminodihydro-1,6-naphthyridinide (5)	KNH ₂ /NH ₃	—	66.1	120.0	124.6	146.1	—	146.6	112.2	156.2	114.0
	$\Delta\delta$	—	88.8	2.7	11.2	6.9	—	0.3	10.0	-5.7	9.8
1,7-Naphthyridine (7)	CDCl ₃	—	152.1	125.2	134.7	119.9	144.0	—	154.5	143.7	131.3
2-Aminodihydro-1,7-naphthyridinide (8)	KNH ₂ /NH ₃	—	65.9	120.2	124.3	120.2	123.8	—	142.6	<i>b</i>	<i>b</i>
	$\Delta\delta$	—	86.2	5.0	10.4	-0.3	20.2	—	11.9		
8-Aminodihydro-1,7-naphthyridinide (9)	KNH ₂ /NH ₃	—	138.2	121.9 ^a	122.5 ^a	80.2	151.8	—	71.0	<i>b</i>	<i>b</i>
	$\Delta\delta$	—	13.9	3.3	12.2	39.7	-7.8	—	83.5		
1,8-Naphthyridine (11)	CDCl ₃	—	153.8	122.3	137.3	137.3	122.3	153.8	—	156.6	123.1
2-Aminodihydro-1,8-naphthyridinide (12)	KNH ₂ /NH ₃	—	67.0	122.1	126.0	131.5	100.8	149.3	—	162.6	112.9
	$\Delta\delta$	—	86.8	0.2	11.3	5.8	21.5	4.5	—	-6.0	10.2
2,6-Naphthyridine (13)	CDCl ₃	152.0	—	144.9	119.3	152.0	—	144.9	119.3	130.3	130.3
1-Aminodihydro-2,6-naphthyridinide (14)	KNH ₂ /NH ₃	68.3	—	152.0	79.3	140.0	—	137.5	121.3	128.3	134.3
	$\Delta\delta$	83.7	—	-7.1	40.0	12.0	—	7.4	-2.0	2.0	-4.0
2,7-Naphthyridine (15)	CDCl ₃	152.9	—	147.1	119.1	119.1	147.1	—	152.9	123.9	138.5
1-Aminodihydro-2,7-naphthyridinide (16)	KNH ₂ /NH ₃	66.7	—	153.8	82.5	111.1	145.4	—	147.0	118.1	142.3
	$\Delta\delta$	86.2	—	-6.7	36.6	8.0	1.7	—	5.9	5.8	-3.8

^a The signals may be interchanged.

^b The signals could not be detected.

density¹⁴ (Table I); therefore position 2 is expected to be most vulnerable to nucleophilic attack of the amide ion. By measuring a solution of **4** in KNH_2/NH_3 by ^1H -NMR spectroscopy at -40°C , it was indeed found that addition of the amide ion takes place only on the "quinolinic" position, yielding σ -adduct 2-aminodihydro-1,6-naphthyridinide (**5**).¹⁵ No indication for addition on the "isoquinolinic" position, which should lead to the formation of 5-aminodihydro-1,6-naphthyridinide (**6**), was found (see Tables II and III).



When the temperature was allowed to increase from -40 to about 10°C , no change of the ^1H - and ^{13}C -NMR spectra was observed,¹⁶ indicating that **5** is also thermodynamically most favored. In σ -adduct **5** there is a notable contribution of the para-para quinoid structure³ (**5b**) because it leads to a considerable negative charge on N-6. This para-para quinoid resonance structure has already been discussed as an important contribution in stabilization of adduct **2** (see Section II,A,1). It explains why adduct **6** is not formed even under conditions that are favorable for thermodynamic control. Apparently the azaallylic contribution (**6b**) is of less importance than the para-para quinoid contribution (**5b**) when a nitrogen is present at position 6.

3. 1,7-Naphthyridine

The ^1H - and ^{13}C -NMR spectra of a solution of **7** in KNH_2/NH_3 measured at -50°C are complex. It was originally suggested that in this solution a mixture of three σ -adducts, 2-amino- (**8**), 6-amino-, and 8-amino-dihydro-1,7-naphthyridinide (**9**), was present.¹⁵ More detailed studies on covalent amination with 6,8-dideutero-1,7-naphthyridine have shown that this suggestion was not correct: the upfield shift value of $\Delta\delta = 3.12$ ppm, originally assigned to H-6 in the 6-amino adduct, must be ascribed to H-5 in **9** (Figure 1).¹⁶ ^{13}C -NMR spectroscopy confirms these results. In fact a mixture of only two adducts, **8** and **9**, is formed when **7** is dissolved in KNH_2/NH_3 .

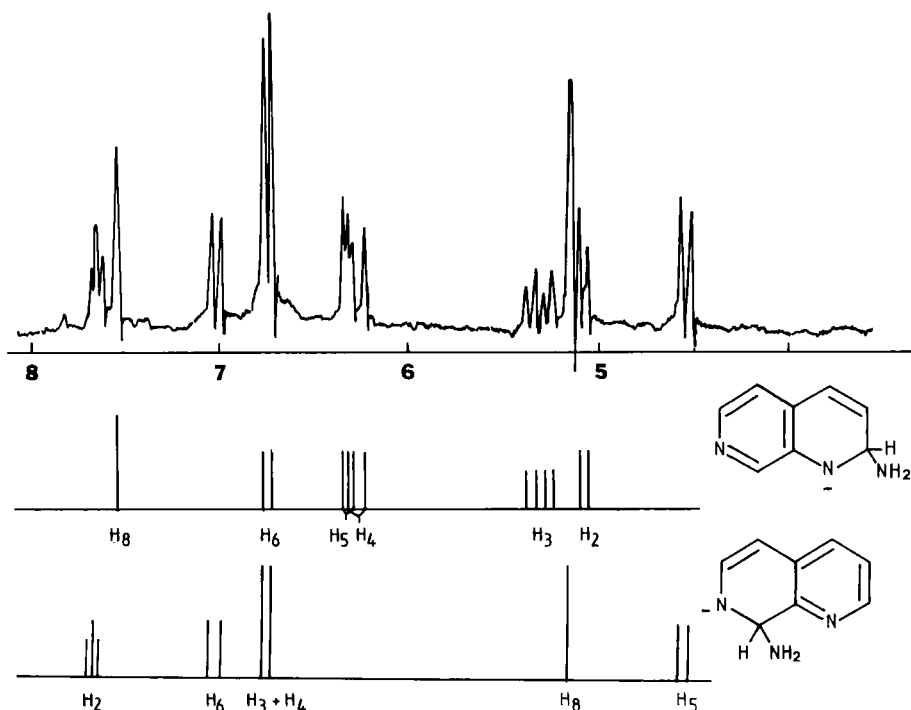
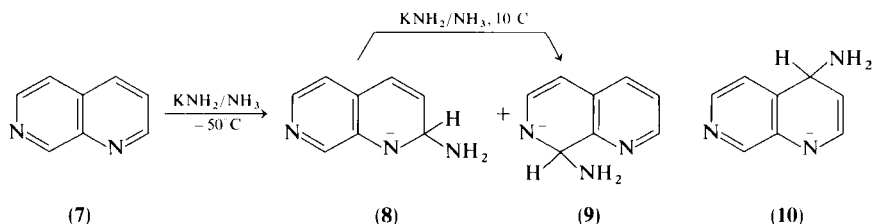


FIG. 1. ^1H -NMR spectrum of a solution of 1,7-naphthyridine (7) in KNH_2/NH_3 .¹⁶

These results are in agreement with electron density calculations, predicting about the same low electron density for positions 2 and 8 and a higher electron density for positions 5 and 6 (Table I).^{13,14,18,19}

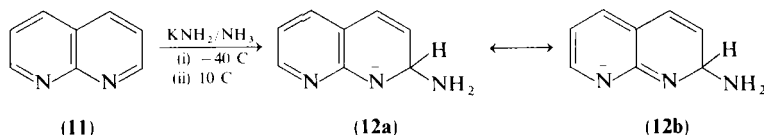


Again, remarkably high $\Delta\delta$ values are found for C-6 and C-8 of σ -adduct **8**¹⁶ (Table III). This indicates once more the importance of para-para and, to a lesser extent, ortho-para quinoid resonance structures.³ On heating the solution of **8** and **9** in KNH_2/NH_3 from -40 to 10°C the mixture irreversibly converts to **9**. The important azaallylic resonance stabilization present in **9** and not in **8** accounts for the higher thermodynamic stability of species **9**.

There is no spectroscopic evidence for the existence of 4-aminodihydro-1,7-naphthyridinide (**10**), although as will be shown, its existence cannot be excluded, on the basis of products obtained in the amination (see Section III,A,3).

4. 1,8-Naphthyridine

Calculations of the electron density on the carbon atoms in the title compound (**11**) show that position 2 (and 7) has the lowest electron density (Table I) and therefore can be expected to have the lowest transition state energy for the charge-controlled addition of the amide ion.^{13,14,18,19} These calculations agree with experiment: upon dissolving **11** in KNH_2/NH_3 at -40°C , the ^1H - and ^{13}C -NMR spectra unequivocally show the presence of only one σ -adduct, 2-aminodihydro-1,8-naphthyridinide (**12**)¹⁵ (see Tables II and III). Increasing the temperature of this solution from -40 to 10°C does not change the ^1H - and ^{13}C -NMR spectra: **12** is still the sole σ -adduct present.¹⁶ No indication for the formation of a C-4 adduct was found.



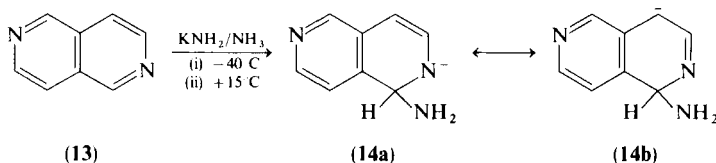
Apparently σ -adduct **12** is kinetically favored and is the thermodynamically more stable one as well. This result is surprising in the light of the results (discussed in Section II,A,1) that the C-4 adduct (**3**), formed from compound **1**, is more stable than the isomeric C-2 adduct (**2**) because of azaallylic stabilization. We assume that the ortho-para resonance contribution (**12b**) adds to the stability of σ -adduct **12**.³ A similar contribution cannot play a role in a σ -adduct on position 4. The importance of ortho-para quinoid resonance structures has already been discussed in Sections II,A,1 and II,A,3.

5. 2,6-Naphthyridine

^1H - and ^{13}C -NMR spectroscopy of a solution of **13** in KNH_2/NH_3 shows that H-1 and C-1 have undergone upfield shifts of 4.24 ppm and 83.7 ppm, respectively (Tables II and III).²⁰ This is due to the formation of 1-aminodihydro-2,6-naphthyridinide (**14**). Because 2,6-naphthyridine is reported to have the lowest electron density at position 1^{18,19} (Table I), the formation of σ -adduct **14** is in good agreement with these calculations. The spectrum of

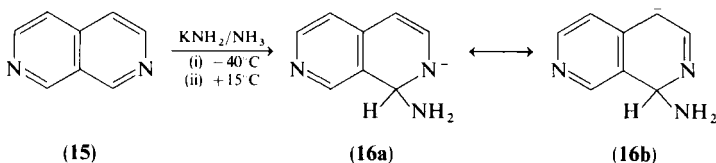
²⁰ H. J. W. van den Haak and H. C. van der Plas, *J. Heterocycl. Chem.* **18**, 1349 (1981).

14 remains essentially unchanged when the temperature is raised to room temperature. Thus **14** is also the thermodynamically most stable adduct. The resonance contribution (**14b**) is important, as experimentally established by the great upfield shifts ($\Delta\delta$) of 40.0 ppm for C-4 and 2.99 ppm for H-4 in **14**, indicating the presence of considerable negative charge on C-4.



6. 2,7-Naphthyridine

From total π -electron density calculations, position 1 in **15** is predicted to be the most vulnerable to a charge-controlled nucleophilic attack (see Table I).^{18,19} Experiment agrees with these predictions, as dissolving **15** in KNH_2/NH_3 at -40°C immediately leads to the formation of 1-amino-dihydro-2,7-naphthyridinide (**16**) as observed by the ^1H - and ^{13}C -NMR spectra²⁰ (Tables II and III). On heating to room temperature no change of the NMR spectra was found. σ -Adduct **16** is resonance stabilized by an important contribution of resonance structure (**16b**) as evidenced by the presence of a considerable upfield shift of C-4 and H-4.



7. Conclusion

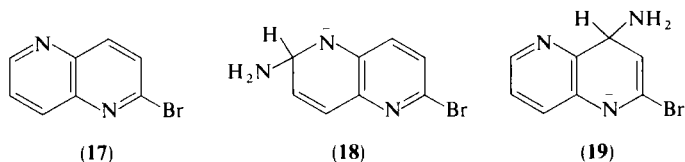
In conclusion, the results of the study on the addition pattern of the amide ion to the 1,X- and 2,X-naphthyridines at low temperature have shown that the addition of the amide ion to the 1,X-naphthyridines ($X = 5, 6$, and 8) always takes place at the "quinolinic" carbon atom (C-2) and that in the 2,X-naphthyridines ($X = 6$ and 7) the "isoquinolinic" carbon atom (C-1) is the preferred site (compare σ -adduct formation of quinoline and isoquinoline¹¹). In case of 1,7-naphthyridine, both the quinolinic position C-2 and the isoquinolinic position C-8 are found to be vulnerable for amide attack. All these vulnerable positions are characterized by having the lowest electron densities of all the carbon positions in the relevant ring systems.

B. COVALENT AMINATION OF SUBSTITUTED NAPHTHYRIDINES

Substituted naphthyridines when reacting with KNH_2/NH_3 often react according to complex reaction pathways: ipso, cine, or tele substitutions, ring-opening reactions, or ring transformations. It is possible to detect by NMR spectroscopy intermediary covalent σ -complexes, often providing useful information on the mechanisms that take place during the several processes. In the following sections we will discuss the covalent σ -adducts formed between substituted naphthyridines and the amide ion or ammonia.

1. Covalent Amination of Halogenonaphthyridines

2-Bromo-1,5-naphthyridine (**17**) forms with potassium amide in liquid ammonia 6-amino-2-bromodihydro-1,5-naphthyridinide (**18**) as evidenced by



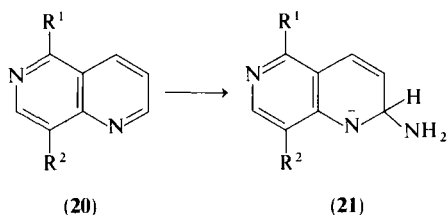
NMR spectroscopy.²¹ The ^1H -NMR spectrum, however, is complex and not all signals could be assigned. The presence of **18** was proved by the appearance of a double doublet at 5.34 ppm (H-7) and a single doublet at 4.94 ppm (H-6). The upfield shift of H-6 ($\Delta\delta = 4.05$ ppm) is in good agreement with the change of the hybridization of C-6 from sp^2 into sp^3 . The ^1H -NMR resonance signals were correctly assigned, as was proven by measuring a solution of 2-bromo-6-deutero-1,5-naphthyridine in KNH_2/NH_3 . The spectrum shows no signal at 4.94 ppm and shows a change of the double doublet at 5.34 ppm into a doublet. By NMR spectroscopy, no addition at C-4 leading to 4-amino-2-bromodihydro-1,5-naphthyridinide (**19**) has been observed, although its existence cannot be doubted because **19** has to be the precursor or 4-amino-1,5-naphthyridine and the ring transformation product 4-amino-2-methyl-1,3,5-triazanaphthalene formed in the reaction (see Section IV).^{22,23}

²¹ H. J. W. van den Haak and H. C. van der Plas, *J. Org. Chem.* **47**, 1673 (1982).

²² W. Czuba, *Recl. Trav. Chim. Pays-Bas* **82**, 997 (1963).

²³ W. Czuba and T. Kowalska, *Rocz. Chem.* **49**, 193 (1975).

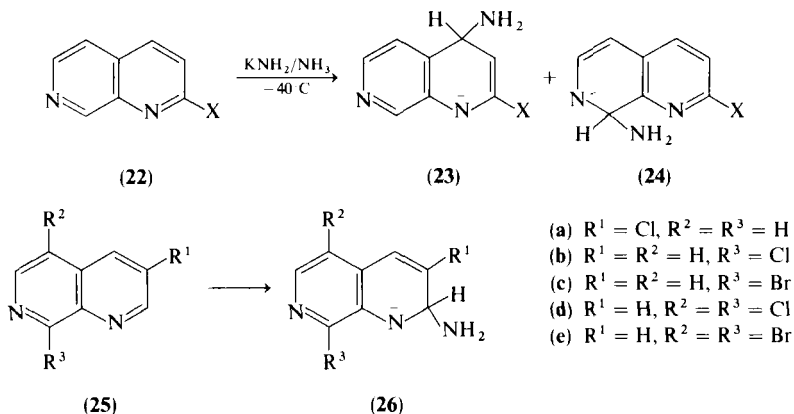
Only three examples of the occurrence of covalent amination of halogeno-1,6-naphthyridines are known: 5-chloro- (**20a**) and 5-bromo-1,6-naphthyridine (**20b**) give exclusively the corresponding 2-aminodihydro-5-halogeno-1,6-naphthyridinides (**21a** and **21b**), and 8-bromo-1,6-naphthyridine (**20c**), with KNH_2/NH_3 gives only 2-aminodihydro-8-bromo-1,6-naphthyridinide (**21c**) (Table IV).²⁴



- (a) $\text{R}^1 = \text{Cl}, \text{R}^2 = \text{H}$
 (b) $\text{R}^1 = \text{Br}, \text{R}^2 = \text{H}$
 (c) $\text{R}^1 = \text{H}, \text{R}^2 = \text{Br}$

Many studies concerning the covalent amination of halogeno-1,7-naphthyridines have been carried out. Addition to C-2, C-4, and C-8 has been found, and the pattern of addition depends on the position of the halogen in the ring.

2-Chloro-1,7-naphthyridine (**22**; $\text{X} = \text{Cl}$) with KNH_2/NH_3 gives a mixture of two adducts, 4-amino- (**23**; $\text{X} = \text{Cl}$) and 8-amino-2-chlorodihydro-1,7-naphthyridinide (**24**; $\text{X} = \text{Cl}$) (Table IV and Fig. 2). From earlier work it was suggested that in addition to **23** ($\text{X} = \text{Cl}$) and **24** ($\text{X} = \text{Cl}$) the isomeric 6-amino-2-chlorodihydro-1,7-naphthyridinide also was formed.²⁵ This



²⁴ H. J. W. van den Haak and H. C. van der Plas, unpublished results.

²⁵ H. C. van der Plas, M. Woźniak, and B. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **96**, 151 (1977).

TABLE IV
¹H-NMR DATA OF SOME HALOGENONAPHTHYRIDINES AND
 THEIR ANIONIC σ -COMPLEXES WITH POTASSIUM AMIDE

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8
5-Chloro-1,6-naphthyridine (20a)	CDCl ₃	—	9.02	7.52	8.48	—	—	8.40	7.76
2-Amino-5-chlorodihydro-1,6-naphthyridine (21a)	KNH ₂ /NH ₃	—	4.98	5.29	6.47	—	—	6.98	5.86
	$\Delta\delta$	—	4.04	2.23	2.01	—	—	1.42	1.90
5-Bromo-1,6-naphthyridine (20b)	CDCl ₃	—	8.99	7.50	8.44	—	—	8.38	7.77
2-Amino-5-bromodihydro-1,6-naphthyridine (21b)	KNH ₂ /NH ₃	—	4.97	5.27	6.40	—	—	6.94	5.85
	$\Delta\delta$	—	4.02	2.23	2.04	—	—	1.44	1.92
8-Bromo-1,6-naphthyridine (20c)	CDCl ₃	—	9.15	7.54	8.25	9.13	—	8.93	—
2-Amino-8-bromodihydro-1,6-naphthyridine (21c)	KNH ₂ /NH ₃	—	5.20	5.33	6.29	7.58	—	7.16	—
	$\Delta\delta$	—	3.95	2.21	1.96	1.55	—	1.77	—
2-Chloro-1,7-naphthyridine (22a)	CDCl ₃	—	—	7.62	8.12	7.72	8.65	—	9.45
4-Amino-2-chlorodihydro-1,7-naphthyridine (23a)	KNH ₂ /NH ₃	—	—	4.65	4.20	7.10	7.72	—	8.02
	$\Delta\delta$	—	—	2.97	3.92	0.62	0.93	—	1.43
8-Amino-2-chlorodihydro-1,7-naphthyridine (24a)	KNH ₂ /NH ₃	—	—	7.02	6.90	4.62	6.75	—	5.20
	$\Delta\delta$	—	—	0.60	1.22	3.10	1.90	—	4.25
3-Chloro-1,7-naphthyridine (25a)	CDCl ₃	—	8.92	—	8.16	7.59	8.67	—	9.54
2-Amino-3-chlorodihydro-1,7-naphthyridine (26a)	KNH ₂ /NH ₃	—	5.20	—	6.52	4.46 ^b	6.92 ^b	—	7.92 ^b
	$\Delta\delta$	—	3.72	—	1.64	1.13	1.75	—	1.62
5-Chloro-1,7-naphthyridine (27a)	CDCl ₃	—	8.99	7.62	8.41	—	8.58	—	9.33
2-Amino-5-chlorodihydro-1,7-naphthyridine (29)	KNH ₂ /NH ₃	—	5.07	5.45	6.63	—	6.67	—	7.55
	$\Delta\delta$	—	3.92	2.17	1.78	—	1.91	—	1.78
8-Amino-5-chlorodihydro-1,7-naphthyridine (28a)	KNH ₂ /NH ₃	—	7.82 ^a	7.04 ^a	7.04 ^a	—	7.10	—	5.07
	$\Delta\delta$	—	1.17	0.58	1.37	—	1.48	—	4.26
8-Chloro-1,7-naphthyridine (25b)	CDCl ₃	—	9.15	7.68	8.25	7.65	8.39	—	—
2-Amino-8-chlorodihydro-1,7-naphthyridine (26b)	KNH ₂ /NH ₃	—	5.15	5.45	6.35	6.45	6.62	—	—
	$\Delta\delta$	—	4.00	2.23	1.90	1.20	1.77	—	—
8-Bromo-1,7-naphthyridine (25c)	CDCl ₃	—	9.10	7.65	8.17	7.60	8.31	—	—
2-Amino-8-bromodihydro-1,7-naphthyridine (26c)	KNH ₂ /NH ₃	—	5.19	5.46	6.37	6.48	6.64	—	—
	$\Delta\delta$	—	3.91	2.19	1.80	1.12	1.67	—	—
5,8-Dichloro-1,7-naphthyridine (25d)	CDCl ₃	—	9.08	7.73	8.45	—	8.33	—	—
2-Amino-5,8-dichlorodihydro-1,7-naphthyridine (26d)	KNH ₂ /NH ₃	—	5.07	5.50	6.53	—	6.53	—	—
	$\Delta\delta$	—	4.01	2.23	1.92	—	1.80	—	—
5,8-Dibromo-1,7-naphthyridine (25e)	CDCl ₃	—	9.08	7.71	8.41	—	8.47	—	—
2-Amino-5,8-dibromodihydro-1,7-naphthyridine (26e)	KNH ₂ /NH ₃	—	5.06	5.47	6.47	—	6.62	—	—
	$\Delta\delta$	—	4.02	2.24	1.94	—	1.85	—	—
2-Chloro-1,8-naphthyridine (30a)	CDCl ₃	—	—	7.50	8.20	8.25	7.53	9.10	—
7-Amino-2-chlorodihydro-1,8-naphthyridine (31a)	KNH ₂ /NH ₃	—	—	5.45	6.52	6.22	5.28	5.10	—
	$\Delta\delta$	—	—	2.05	1.68	2.03	2.25	4.00	—
2-Bromo-1,8-naphthyridine (30b)	CDCl ₃	—	—	7.59	8.05	8.21	7.52	9.10	—
7-Amino-2-bromodihydro-1,8-naphthyridine (31b)	KNH ₂ /NH ₃	—	—	5.63	6.48	6.26	5.36	5.10	—
	$\Delta\delta$	—	—	1.96	1.57	1.95	2.16	4.00	—
3-Chloro-1,8-naphthyridine (30c)	CDCl ₃	—	8.97	—	8.12	8.12	7.47	9.07	—
2-Amino-3-chlorodihydro-1,8-naphthyridine (32)	KNH ₂ /NH ₃	—	5.27	—	6.50	6.78 ^b	5.77 ^b	7.75 ^b	—
	$\Delta\delta$	—	3.70	—	1.62	1.34	1.70	1.32	—
1-Chloro-2,6-naphthyridine (33a)	CDCl ₃	—	—	8.40	7.57	9.28	—	8.75	7.93
5-Amino-1-chlorodihydro-2,6-naphthyridine (34a)	KNH ₂ /NH ₃	—	—	7.42	6.84	5.01	—	7.21	4.74
	$\Delta\delta$	—	—	0.98	0.73	4.27	—	1.54	3.19
1-Bromo-2,6-naphthyridine (33b)	CDCl ₃	—	—	8.39	7.68	9.23	—	8.73	7.91
5-Amino-1-bromodihydro-2,6-naphthyridine (34b)	KNH ₂ /NH ₃	—	—	7.44	6.90	5.01	—	7.27	4.75
	$\Delta\delta$	—	—	0.95	0.78	4.22	—	1.46	3.16
1-Chloro-2,7-naphthyridine (35a)	CDCl ₃	—	—	8.38	7.54	7.62	8.73	—	9.61
8-Amino-1-chlorodihydro-2,7-naphthyridine (36a)	KNH ₂ /NH ₃	—	—	7.37	6.24	4.68	7.23	—	5.36
	$\Delta\delta$	—	—	1.01	1.30	2.94	1.50	—	4.25
1-Bromo-2,7-naphthyridine (35b)	CDCl ₃	—	—	8.36	7.52	7.52	8.71	—	9.58
8-Amino-1-bromodihydro-2,7-naphthyridine (36b)	KNH ₂ /NH ₃	—	—	7.37	6.28	4.68	7.27	—	5.31
	$\Delta\delta$	—	—	0.99	1.24	2.84	1.43	—	4.27

^a These signals show deceptive simplicity.

^b Assignments of these peaks are uncertain.

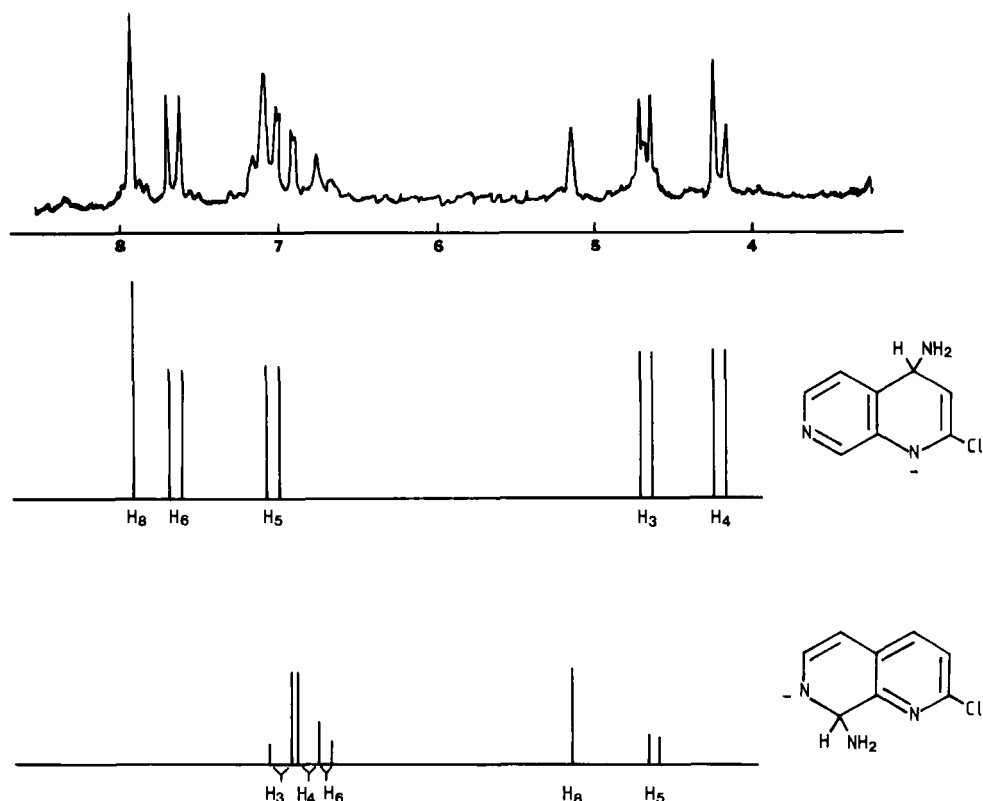


FIG. 2. ¹H-NMR spectrum of a solution of 2-chloro-1,7-naphthyridine (**22**) in KNH₂/NH₃.²⁴

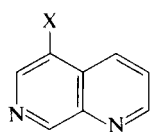
suggestion was made on the basis of the appearance of a doublet at 4.62 ppm; this was ascribed to H-6, which was attached to the tetrahedral C-6 in the 6-amino adduct. However, it has been shown that this assignment was not correct.²⁴ It was found that H-5 in **24** (X = Cl) can also undergo a considerable upfield shift (about 3 ppm) due to azaallylic stabilization. Therefore, the resonance signal at 4.62 ppm must be ascribed to H-5 in **24** (X = Cl) and not to H-6 in the 6-amino adduct.

3-Chloro-,²⁶ 8-chloro-,^{10,25} 8-bromo-,²⁵ 5,8-dichloro, and 5,8-dibromo-1,7-naphthyridine (**25a-e**)²⁷ with KNH₂/NH₃ give an exclusive addition at C-2, yielding the 2-aminochloro- and 2-aminobromodihydro-1,7-naph-

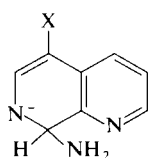
²⁶ H. C. van der Plas, M. Woźniak, and B. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **95**, 233 (1976).

²⁷ M. Woźniak and H. C. van der Plas, unpublished results.

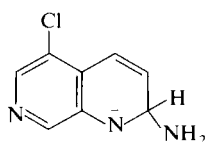
thyridinides (**26a–e**) (Table IV). The addition of the amide ion to C-2 in **25a** (proved by $^1\text{H-NMR}$ spectroscopy of some deuterio derivatives) is of considerable interest, especially in relationship to the question of whether σ -adduct **26a** is the precursor of 3,4-dihydro-1,7-naphthyridine, which is the intermediate formed during reaction of **25a** with KNH_2/NH_3 (see Section III,B,1,c). 5-Bromo-1,7-naphthyridine (**27b**) with KNH_2/NH_3 gives an exclusive addition at C-8, yielding **28b**, whereas 5-chloro-1,7-naphthyridine (**27a**) yields a mixture of C-8 adduct **28a** and C-2 adduct **29**.²⁸



(27)



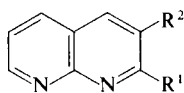
(28)



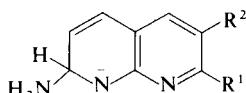
(29)

(a) X = Cl

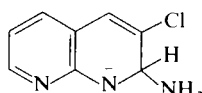
(b) X = Br



(30)



(31)



(32)

(a) $\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{H}$ (b) $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{H}$ (c) $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Cl}$

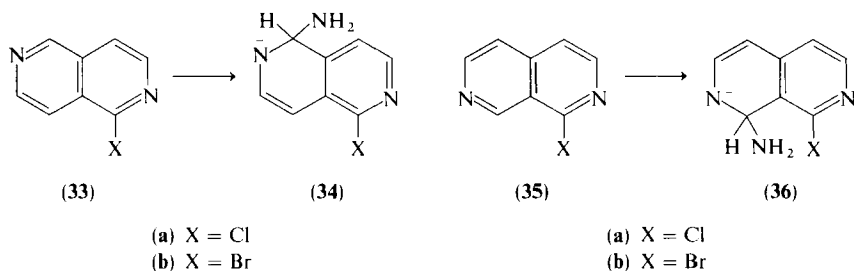
In the 1,8-naphthyridine series similar results have been found: 2-chloro- (**30a**) and 2-bromo-1,8-naphthyridines (**30b**) react with KNH_2/NH_3 to give the C-7 σ -adducts **31a** and **31b**, respectively (Table IV), and 3-chloro-1,8-naphthyridine (**30c**) undergoes addition with an amide ion at C-2, and thus at a position adjacent to the carbon attached to the chloro atom, yielding **32** (Table IV).^{10,29}

The 1-chloro- and 1-bromo-2,6-naphthyridines (**33a** and **33b**)²¹ and the 1-chloro- and 1-bromo-2,7-naphthyridines (**35a** and **35b**)³⁰ have been reported to give, with KNH_2/NH_3 , an exclusive addition of the amide ion on the "isoquinolinic" position, yielding σ -adducts **34a**, **34b**, **36a**, and **36b**, respectively (Table IV).

²⁸ M. Woźniak and H. C. van der Plas, *J. Heterocycl. Chem.* **15**, 731 (1978).

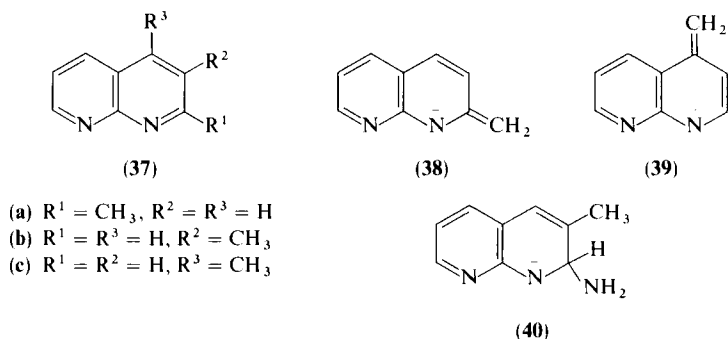
²⁹ H. C. van der Plas, M. Woźniak, and B. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **97**, 130 (1978).

³⁰ J. H. W. van den Haak and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, submitted for publication.



2. Covalent Amination of Methyl-1,8-naphthyridines

There is only one study concerning the covalent amination of methyl-naphthyridines. It has been reported that both 2-methyl- (37a) and 4-methyl-1,8-naphthyridine (37c) after treatment with KNH_2/NH_3 are not converted into 1:1 σ -adducts but instead into their conjugate bases 38 and 39, respec-



tively.¹⁵ The resonance signals of all ring hydrogen atoms and ring carbon atoms are shifted upfield (Table V), but the upfield shifts do not exceed 2 ppm for the hydrogen atoms and 18 ppm for the carbon atoms. (Compare the magnitude of the upfield shifts for adduct formation in Tables II and III.) Convincing proof for the existence of anions 38 and 39 is provided by the ^{13}C -NMR signals of the methylene side chain. They show a considerable downfield shift of 50.5–57.1 ppm in comparison to the carbon signals of the methyl group when 37a and 37c are measured in CDCl_3 . Moreover the ^1H -NMR signals of the hydrogens of the side chain are present as a pair of doublets.¹⁵ These doublets are explained by restricted rotation around the aromatic carbon to methylene carbon bond; the methylene hydrogens are in different chemical environments. Amide-induced deprotonation of a methyl group α or γ to the ring nitrogen is well established, and NMR data

TABLE V
¹H- AND ¹³C-NMR DATA OF 2-, 3-, AND 4-METHYL-1,8-NAPHTHYRIDINES IN DEUTEROCHLOROFORM AND IN
 LIQUID AMMONIA CONTAINING POTASSIUM AMIDE

Compound	Solvent	¹ H-NMR chemical shift (δ)							¹³ C-NMR chemical shift (δ)								
		H-2	H-3	H-4	H-5	H-6	H-7	H ^a	C-2	C-3	C-4	C-5	C-6	C-7	C-9	C-10	C ^a
2-Methyl-1,8-naphthyridine (37a) Anion (38)	CDCl ₃		7.25	7.97	8.03	7.32	9.00	2.75	163.0	123.0	137.0 ^b	136.8 ^b	121.4	153.3	156.2	120.9	25.6
	KNH ₂ /NH ₃		6.00	6.25	6.69	5.83	7.60	3.05 3.30	158.4	125.9	128.1	131.4	107.0	149.4	163.7	117.4	76.1
	Δδ		1.25	1.72	1.34	1.49	1.40	−0.30 −0.55	4.6	−2.9	8.9	5.4	14.4	3.9	−7.5	3.5	−50.5
3-Methyl-1,8-naphthyridine (37b)	CDCl ₃	8.98		7.94	8.12	7.45	9.07	2.55	155.5	131.9	135.6	136.6	122.2	152.6	155.0	122.5	18.4
2-Amino-3-methyldihydro-1,8-naphthyridinide (40)	KNH ₂ /NH ₃	5.02		6.00	6.55	5.59	7.48	1.90	71.4	130.5	121.8	129.9	101.0	148.1	162.2	113.8	21.0
	Δδ	3.96		1.94	1.57	1.86	1.59	0.65	84.1	1.4	13.8	6.7	21.2	4.5	−7.2	8.7	−2.6
4-Methyl-1,8-naphthyridine (37c) Anion (39)	CDCl ₃	8.87	7.15	—	8.17	7.35	9.01	2.56	153.1	122.7	145.9	133.4	121.7	153.0	156.2	122.7	17.6
	KNH ₂ /NH ₃	6.72	5.35	—	7.70	6.42	8.02	3.52 3.58	145.7	104.5	145.2	131.3	112.2	149.3	162.7	119.1	74.7
	Δδ	2.15	1.80	—	0.47	0.93	0.99	−0.96 −1.29	7.4	18.2	0.7	2.1	9.5	3.7	−6.5	3.6	−57.1

^a Side chain.

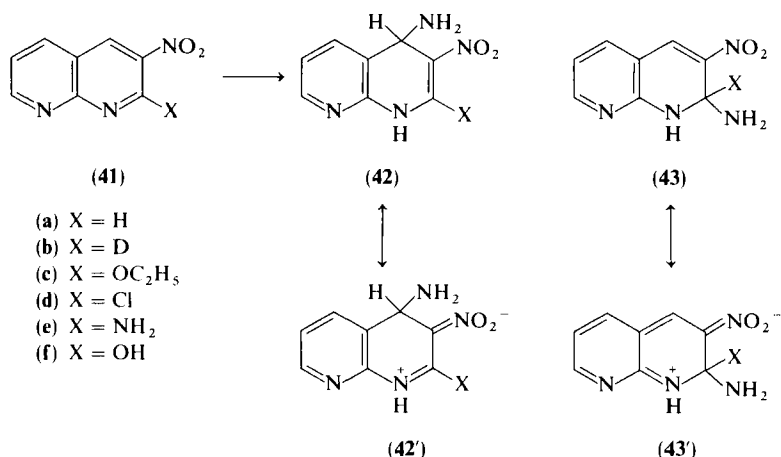
^b These signals may be interchanged.

of the conjugate base of 4-methylpyrimidine,³¹ 4-methyl-5-bromopyrimidine,³¹ and 2-methylpyridine³² are recorded.

However, 3-methyl-1,8-naphthyridine (**37b**) reacts with KNH_2/NH_3 in a completely different way than do **37a** and **37c**.¹⁵ ^1H - and ^{13}C -NMR spectroscopy unequivocally show the formation of the 1:1 σ -adduct 2-amino-3-methyldihydro-1,8-naphthyridinide (**40**) (Table V). No addition at C-7 is observed, although this position is also vulnerable to nucleophilic attack (see Section II,A,4). Similar behavior has been found in the Chichibabin amination of 3-methylpyridine; the amide predominantly attacks C-2 and not C-6.³³ This result has been explained by an ion dipole attraction between the incoming amide ion and the methyl substituent.³⁴ This type of attractive interaction also possibly determines the attack on C-2 in **37b**.

3. Covalent Amination of Nitro-1,X-naphthyridines

Studies have been made of the covalent amination of 3-nitro-1,X-naphthyridines ($X = 5,6$, and 8).^{27,35} In contrast to the parent systems and their halogen and methyl derivatives, 3-nitronaphthyridines undergo covalent amination with weak nucleophilic liquid ammonia at -45°C . The electrophilic character of the naphthyridine system is enhanced by the presence of the nitro group. 3-Nitro-1,8-naphthyridine (**41a**) undergoes addition at



³¹ J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas, and B. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas* **93**, 231 (1974).

³² J. A. Zoltewicz and L. S. Helmick, *J. Org. Chem.* **38**, 658 (1973).

³³ R. A. Abramovitch, F. Helmer, and J. G. Saha, *Chem. Ind. (London)*, 659 (1964); *Can. J. Chem.* **43**, 725 (1965).

³⁴ R. A. Abramovitch, F. Helmer, and M. Liveris, *J. Org. Chem.* **34**, 1730 (1969).

³⁵ M. Woźniak, H. C. van der Plas, and B. van Veldhuizen, *J. Heterocycl. Chem.*, in press.

position 4 when dissolved in liquid ammonia, yielding 4-amino-1,4-dihydro-3-nitro-1,8-naphthyridine (**42a**)³⁵ (Table VI), as shown by the ¹H-NMR spectrum of 2-deutero-3-nitro-1,8-naphthyridine (**41b**). No change of the ¹H-NMR spectrum of **41a** in liquid ammonia was observed from -45 to +20°C. Thus, σ -adduct **42** is kinetically favored and is also the most thermodynamically stable one.

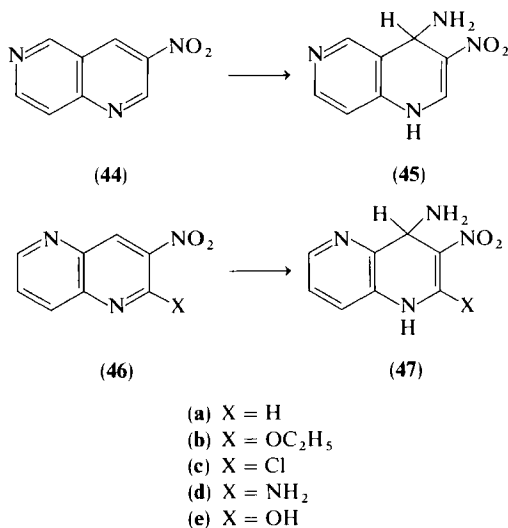
TABLE VI
¹H-NMR DATA OF THE RING HYDROGENS OF SOME NITRONAPHTHYRIDINES
AND THEIR σ -ADDUCTS WITH AMMONIA

Compound	Solvent	H-2	H-4	H-5	H-6	H-7	H-8
3-Nitro-1,5-naphthyridine (46a)	DMSO	9.68	9.17	—	9.20	8.02	8.63
4-Amino-3-nitro-1,4-dihydro-1,5-naphthyridine (47a)	NH ₃	8.41	5.36	—	8.25	7.27	7.55
	$\Delta\delta$	1.21	3.81	—	0.95	0.75	1.08
2-Ethoxy-3-nitro-1,5-naphthyridine (46b)	CDCl ₃	—	8.65	—	8.82	7.58	8.10
4-Amino-2-ethoxy-3-nitro-1,4-dihydronaphthyridine (47b)	NH ₃	—	5.42	—	8.18	7.26	7.40
	$\Delta\delta$	—	3.23	—	0.64	0.32	0.70
2-Chloro-3-nitro-1,5-naphthyridine (46c)	CDCl ₃	—	8.83	—	9.09	7.78	8.39
4-Amino-2-chloro-3-nitro-1,4-dihydro-1,5-naphthyridine (47c)	NH ₃	—	5.37	—	8.28	7.30	7.52
	$\Delta\delta$	—	3.46	—	0.81	0.48	0.87
2-Amino-3-nitro-1,5-naphthyridine (46d)	DMSO	—	8.88	—	8.71	7.66	7.93
2,4-Diamino-3-nitro-1,4-dihydro-1,5-naphthyridine (47d)	NH ₃	—	5.31	—	7.98	7.15	7.15
	$\Delta\delta$	—	3.57	—	0.73	0.51	0.78
3-Nitro-1,5-naphthyridin-2[1H]-one (46e)	DMSO	—	8.00	—	8.23	7.29	7.47
4-Amino-3-nitro-1,4-dihydro-1,5-naphthyridin-2[1H]-one (47e) ^a	NH ₃	—	5.45	—	8.15	7.31	7.31
	$\Delta\delta$	—	2.55	—	0.08	-0.02	0.16
3-Nitro-1,6-naphthyridine (44)	CDCl ₃	9.82	9.18	9.51	—	8.98	0.08
4-Amino-3-nitro-1,4-dihydro-1,6-naphthyridine (45)	NH ₃	8.45	5.10	8.45	—	8.21	7.00
	$\Delta\delta$	1.37	4.08	1.06	—	0.77	1.08
3-Nitro-1,8-naphthyridine (41a)	DMSO	9.74	9.52	8.83	7.88	9.30	—
4-Amino-3-nitro-1,4-dihydro-1,8-naphthyridine (42a)	NH ₃	8.57	5.14	7.82	7.07	8.30	—
	$\Delta\delta$	1.17	4.38	1.01	0.81	1.00	—
2-Ethoxy-3-nitro-1,8-naphthyridine (41c)	CDCl ₃	—	8.63	8.22	7.45	9.08	—
4-Amino-2-ethoxy-3-nitro-1,4-dihydro-1,8-naphthyridine (42c)	NH ₃	—	5.16	7.71	6.97	8.20	—
	$\Delta\delta$	—	3.47	0.51	0.48	0.88	—
2-Chloro-3-nitro-1,8-naphthyridine (41d)	DMSO	—	9.43	8.72	7.85	9.27	—
4-Amino-2-chloro-3-nitro-1,4-dihydro-1,8-naphthyridine (42d)	NH ₃	—	5.18	7.78	7.10	8.28	—
	$\Delta\delta$	—	4.25	0.94	0.75	0.99	—
2-Amino-3-nitro-1,8-naphthyridine (41e)	DMSO	—	9.20	8.38	7.32	8.92	—
2,4-Diamino-3-nitro-1,4-dihydro-1,8-naphthyridine (42e)	NH ₃	—	5.06	7.59	6.75	8.07	—
	$\Delta\delta$	—	4.14	0.79	0.57	0.85	—
3-Nitro-1,8-naphthyridin-2[1H]-one (41f)	DMSO	—	8.93	8.33	7.37	8.68	—
4-Amino-3-nitro-1,4-dihydro-naphthyridin-2[1H]-one (42f)	NH ₃	—	5.16	7.75	6.92	8.06	—
	$\Delta\delta$	—	3.77	0.58	0.45	0.62	—

^a Mixture of adduct and starting material.

σ -Adduct **42** is more stable than the isomeric C-2 adduct **43**, which has been explained by the fact that resonance structure **42'** provides a more important contribution to stabilization of $\mathbf{42} \leftrightarrow \mathbf{42'}$ than the resonance contribution of $\mathbf{43'}$ to $\mathbf{43} \leftrightarrow \mathbf{43'}$ (in **42'** one aromatic 6π -electron system is maintained and **43'** the aromaticity is lost). Moreover, neutral species **43** cannot be stabilized by charge delocalization in an ortho-para quinoid resonance structure, as has been advocated for anionic σ -adduct **12**.¹⁶ Introduction of electron-donating or electron-attracting substituents in position 2 does not change the addition pattern: the 2-substituted 3-nitro-1,8-naphthyridines (**41c-f**) give exclusive addition at C-4 when dissolved in liquid ammonia (Table VI). When position 4 is occupied, no addition at C-2 or at any other carbon position takes place, as evidenced by the fact that 4-amino-3-nitro-1,8-naphthyridine does not undergo addition at C-2 with liquid ammonia.

Similar behavior was observed with 3-nitro-1,6-naphthyridine (**44**), 3-nitro-1,5-naphthyridine (**46a**), and some of its derivatives (**46b-e**),²⁷ which



undergo addition at position 4, yielding σ -adducts **45** and **47**, respectively (Table VI).

For the same reasons as discussed for the 3-nitro-1,8-naphthyridines, addition at C-4 is strongly promoted. If position 4 is occupied, no addition takes place: 4-amino-3-nitro-1,6- and -1,5-naphthyridine do not undergo addition at C-2 when subjected to treatment with liquid ammonia. It is interesting that **46a** does not undergo covalent hydration in neutral nor in acidic medium.⁹

III. Replacement Reactions with Nitrogen Nucleophiles

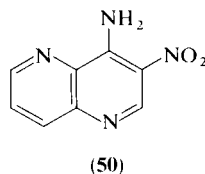
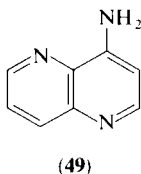
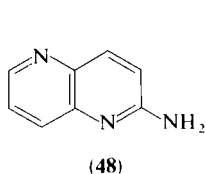
A. REPLACEMENT OF HYDROGEN BY AN AMINO GROUP (CHICHIBABIN AMINATION)

Chichibabin amination refers to a reaction in which a hydrogen of an azaheteroarene is replaced by an amino group. The reaction is usually carried out by heating the heterocycle with a metal amide at elevated temperatures in an aprotic inert solvent. Potassium amide or sodium amide in liquid ammonia have also been found to be appropriate reagents for amination; the presence of an oxidant seems to promote the reaction. Potassium nitrate is usually employed as an oxidant,^{19,36} but other work shows that potassium permanganate can also successfully be used as an oxidizing agent in liquid ammonia.^{16,20,37}

The mechanism of the Chichibabin amination of pyridine has been discussed in terms of an addition-elimination mechanism via a covalent σ -adduct.^{38,39} The possible formation of 2,3-didehydropyridine (2,3-pyridyne) as intermediate in the Chichibabin amination has been advocated, but this is now definitely rejected.^{38,39} In this section we discuss the Chichibabin amination of the parent naphthyridines and their derivatives and the products that are obtained in these aminations. The formation of their precursors (the covalent σ -adducts) has already been discussed in Section II,A and II,B.

1. Amination of 1,5-Naphthyridines

Amination of 1,5-naphthyridine (**1**) with sodamide in liquid ammonia at room temperature was reported by Hart⁴⁰ to give 2-amino-1,5-naphthyridine (**48**). Other work has shown that under the conditions described by Hart,



³⁶ F. W. Bergström, *Justus Liebigs Ann. Chem.* **515**, 34 (1935).

³⁷ A. D. Counotte-Potman and H. C. van der Plas, *J. Heterocycl. Chem.* **18**, 123 (1981).

³⁸ R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.* **6**, 229 (1966).

³⁹ A. F. Pozharskii, A. M. Simonov, and V. N. Doron'kin, *Usp. Khim.*, (*Engl. Transl.*) **47**, 1933 (1978).

⁴⁰ E. P. Hart, *J. Chem. Soc.*, 1879 (1954).

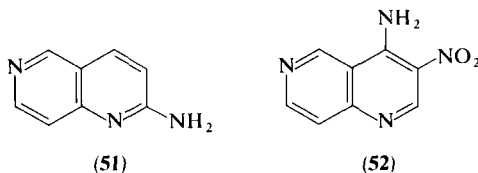
the amination could not be duplicated.^{19,41} Amination of **1** under modified conditions (potassium amide in liquid ammonia at room temperature) was successful¹⁹; it was thought to give the same product as described by Hart. However, the structure of the amino compound obtained in these reactions appeared to be incorrect; the actual compound formed in these aminations was not **48** but instead the 4-amino-1,5-naphthyridine (**49**).⁴¹ When the reaction was carried out at higher temperature (50°C) the yield of **49** was considerably improved (80%).^{5,50}

As we have seen in Section II,A,1 the formation of the 2-amino σ -adduct (**2** and **3**) from **1** and potassium amide in liquid ammonia is strongly dependent on the temperature. At low temperature (-40°C) adduct **2** and at room temperature adduct **3** have been obtained.^{15,16} These results explain why under the reaction conditions used by Paudler and Kress¹⁹ **49**, with **3** as its precursor, and not **48**, was formed. In accordance with covalent amination studies, amination of **1** with KNH_2/NH_3 in the presence of potassium permanganate at -40°C gave the 2-amino compound **48** in 36% yield.¹⁶ The procedure, involving amination at 10°C followed by cooling to -40°C and subsequently adding potassium permanganate, gave minor yields of **49**.

Other work has been carried out concerning the amination of 3-nitro-1,5-naphthyridine (**46a**) with liquid ammonia containing potassium permanganate.²⁷ The 4-amino-3-nitro-1,5-naphthyridine (**50**) is obtained in 50% yield. Its precursor, the covalent σ -adduct (**47a**), has been detected by NMR spectroscopy (see Section II,B,3).

2. Amination of 1,6-Naphthyridines

Chichibabin amination of 1,6-naphthyridine (**4**) with KNH_2/NH_3 at room temperature gives 2-amino-1,6-naphthyridine (**51**) in 33% yield.¹⁹ When the



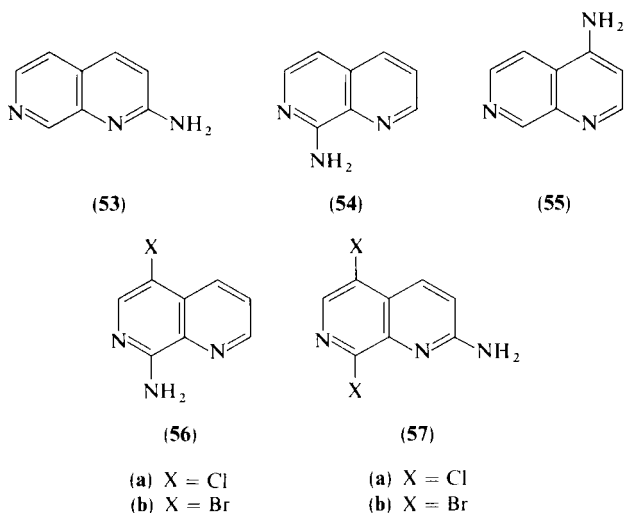
reaction was carried out at $+50^{\circ}\text{C}$, the same product (**51**) was obtained^{5,50}; however, the yield was considerably higher (83%). Potassium permanganate was successfully used as an oxidizing agent in the amination of **4** with KNH_2/NH_3 at -40°C giving **51** (40%).¹⁶ These results are in good agreement with the results obtained in the covalent amination studies of **4**, showing that at

⁴¹ E. V. Brown and A. C. Plas, *J. Heterocycl. Chem.* **7**, 593 (1970).

a low temperature, as at a more elevated one, the amide ion always adds to C-2, yielding the 2-amino σ -adduct (**5**) (see Section II,A,2). 3-Nitro-1,6-naphthyridine (**44**) has been successfully aminated to 4-amino-3-nitro-1,6-naphthyridine (**52**) on treatment with liquid ammonia containing potassium permanganate.²⁷ The existence of the intermediate species 4-amino-3-nitro-1,4-dihydro-1,6-naphthyridine (**45**) has been proved by NMR spectroscopy (see Section II,B,3)

3. Amination of 1,7-Naphthyridines

Treatment of 1,7-naphthyridine (**6**) with KNH_2/NH_3 at -45°C gave a mixture of 2-amino- (**53**) and 8-amino-1,7-naphthyridine (**54**)²⁸ (total yield was 8%). When the amination was carried out at room temperature only **54** was formed (yield 37%).¹⁹ These results are in good agreement with NMR studies (see Section II,A,3), which show that the 2-amino adduct (**8**) and the 8-amino adduct (**9**) are formed at low temperature and that σ -adduct **9** is exclusively formed at higher temperature.¹⁶



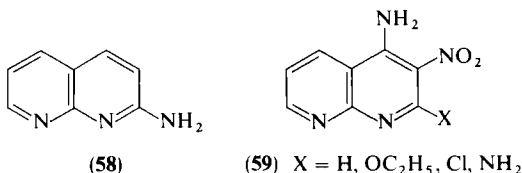
Addition of potassium permanganate to a solution of **6** in KNH_2/NH_3 at -40°C did improve the yields of **53** and **54** considerably (26% and 19%, respectively)¹⁶; however, some 4-amino-1,7-naphthyridine (**55**: 10%) was also found unexpectedly. The formation of **55** suggests the intermediacy of 4-aminodihydro-1,7-naphthyridinide (**10**), although no indication for its existence has been found by NMR spectroscopy.

There are some preliminary unpublished results showing that by reacting 5-chloro- (**27a**) or 5-bromo-1,7-naphthyridine (**27b**) in liquid ammonia with

potassium permanganate, the corresponding 8-amino-5-chloro- (**56a**) and 8-amino-5-bromo-1,7-naphthyridine (**56b**) are formed.²⁷ Furthermore, 5,8-dichloro- (**25d**) and 5,8-dibromo-1,7-naphthyridine (**25e**) were found to give (according to the same procedure) 2-amino-5,8-dichloro (**57a**) and 2-amino-5,8-dibromo-1,7-naphthyridine (**57b**).²⁷

4. Amination of 1,8-Naphthyridines

The product obtained in the amination of 1,8-naphthyridine (**11**) with KNH_2/NH_3 is found to be independent of the temperature of the reaction. At room temperature only 2-amino-1,8-naphthyridine (**58**) is formed (29%)¹⁹; at 50°C **58** is also the sole compound,^{5,50} in increased yield (78%). These

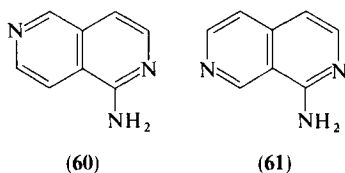


results are in good accordance with electron density calculations, which predict that position 2 has the lowest electron density,^{13,14,18,19} and with NMR studies on covalent amination^{15,16} (see Section II,A,4). Addition of potassium permanganate to a solution of **11** in KNH_2/NH_3 at -40°C gave **58** as expected, but the yield was poor (10%).¹⁶

Successful aminations were reported on treatment of a solution of 3-nitro-2-X-1,8-naphthyridines (**41**) with potassium permanganate, the 4-amino-3-nitro-2-X-1,8-naphthyridines (**59**) being obtained in 50–80% yields.³⁵ The precursors of **59**, i.e., σ -adducts **42a–e**, have been identified by NMR spectroscopy (see Section II,B,3).

5. Amination of 2,6- and 2,7-Naphthyridines

The preparation of 1-amino-2,6-naphthyridine²⁰ (**60**) and 1-amino-2,7-naphthyridine⁴² (**61**) in yields of 23% and 56%, respectively, has been

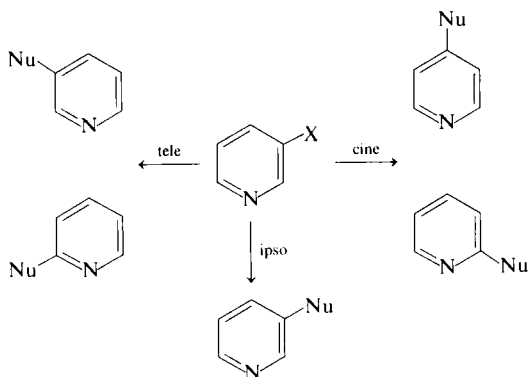


⁴² W. W. Paudler and S. J. Cornrich, *J. Heterocycl. Chem.* **7**, 419 (1970).

achieved by reacting 2,6-naphthyridine (**13**) and 2,7-naphthyridine (**15**) with KNH_2/NH_3 at room temperature. Addition of potassium permanganate did not improve the yields.²⁰ The results of the amination are in good agreement with electron density calculations^{13,14,18,19} and with NMR studies on the formation of the precursors of both amino compounds²⁰ (see Sections II,A,5 and II,A,6).

B. REPLACEMENT OF HALOGEN BY AN AMINO GROUP

The nucleophilic displacement of halogen in halogenoazaheteroarenes is a subject of continuous study because of its potential application in synthetic chemistry; detailed studies on mechanistic aspects have also been carried out.⁴³ From these extensive studies it is evident that nucleophilic displacements in azaheterocycles can occur according to a number of different pathways. One is the very common ipso substitution, which describes a reaction in which the nucleophile (Nu) is found in the product at the same position as that which the leaving group X was attached to in the substrate. In addition to ipso substitutions, cine and tele substitutions also can take place. A substitution is cine if in the product the nucleophile occupies a position that is adjacent to the one from which the leaving group in the substrate has departed. A substitution leading to a product in which the nucleophile is present on a position that is more than one position removed from that occupied by the leaving group in the substrate, is called a tele substitution. These three different types of substitutions are exemplified as follows.



In the reaction of halogenonaphthyridines with potassium amide in liquid ammonia all three different replacement reactions are found. In Section

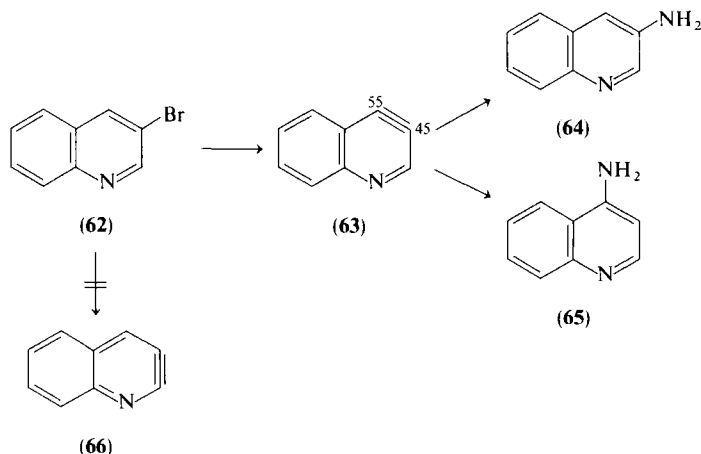
⁴³ H. C. van der Plas, *Lect. Heterocycl. Chem.* **2**, S-83 (1974).

III,B,1 we will deal with reactions in which both cine and ipso products are formed. The mechanism according to which these products are formed has been explained by the occurrence of a didehydronaphthyridine (naphthyridyne) intermediate.⁴⁴ In Section III,B,2 the occurrence of aminodehalogenations involving tele substitutions are discussed and in Section III,B,3 the reactions in which the aminodehalogenation occurs in an ipso position are examined.

1. Amino Dehalogenations Involving Didehydronaphthyridines as Intermediates

There is ample evidence suggesting that a halogenonaphthyridine can react with KNH_2/NH_3 by a dihydronaphthyridine as intermediate. Because an analogy exists between the chemistry of halogenonaphthyridines and halogenoquinolines (and halogenoisoquinolines), we briefly summarize studies of the behavior of the halogeno derivatives of quinoline and isoquinoline toward KNH_2/NH_3 prior to a more detailed discussion of the reactions of halogenonaphthyridines.

Reaction of 3-bromoquinoline (**62**) with KNH_2/NH_3 gave a mixture of the ipso product 3-aminoquinoline (**64**) and the cine product 4-aminoquinoline



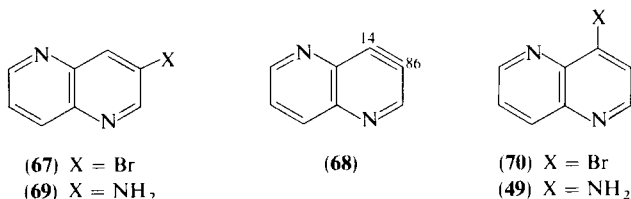
⁴⁴ For reviews on this subject, see H. J. den Hertog and H. C. van der Plas, *Adv. Heterocycl. Chem.* **4**, 121 (1965); T. Kauffmann, *Angew. Chem. Int. Ed. Engl.* **4**, 543 (1965); R. W. Hoffmann, "Dehydrobenzene and Cycloalkenes," p. 275. Academic Press, New York, 1967; H. J. den Hertog and H. C. van der Plas, in "Chemistry of Acetylenes" (H. G. Viehe, ed.), p. 1149. Dekker, New York, 1969; T. Kauffmann and R. Wirthwein, *Angew. Chem., Int. Ed. Engl.* **10**, 20 (1971); M. G. Reinecke, in "Reactive Intermediates" (R. A. Abramovitch, ed.), Vol. 2, Chap. 5, Plenum, New York, 1981.

(65) in a ratio of 45:55.⁴⁵ 3,4-Didehydroquinoline (63) is proposed as an intermediate, which underwent addition of the amide ion (or ammonia) at C-4 as well as at C-3. No indication for the occurrence of 2,3-didehydroquinoline (66) was found. If 66 had been an intermediate in the reaction, then it would have led to the formation of 2-aminoquinoline. These and many other studies unambiguously show that 1-aza-2,3-didehydroheteroarenes are never obtained in reactions of 1-aza-2- or 1-aza-3-halogenoheteroarenes with KNH_2/NH_3 . In the light of these results it is not surprising that in reaction of 3- or 4-halogenoisquinolines with KNH_2/NH_3 , no indication for the intermediacy of 3,4-didehydroisoquinoline has been found.^{46,47}

The formation of the didehydro intermediate (63) occurs in two steps: formation of the 3-bromoquinolyl-4-anion by deprotonation at position 4, followed by elimination (E) of the leaving group at C-3. The products are formed by addition (A) of the amide and/or ammonia at C-3 and C-4. Thus, both amino compounds are formed in an EA process: 4-aminoquinoline in an $\text{S}_{\text{N}}(\text{EA})^{\text{cine}}$ process and the 3-aminoquinoline in an $\text{S}_{\text{N}}(\text{EA})^{\text{ipso}}$ substitution.

Extensive investigations have been carried out in order to establish the intermediary occurrence of didehydro-1,5-, -1,6-, -1,7-, and -1,8-naphthyridines in aminations of halogenonaphthyridines with potassium amide in liquid ammonia. These studies have definitively proved that 3,4-didehydro-1, X-naphthyridines (X = 5, 6, 7, 8) are intermediates in aminations of the 3- and 4-bromo (chloro) derivatives of the 1,X-naphthyridines.^{22, 29, 48-50} No evidence has been found for the occurrence of 2,3-didehydro-1,X-naphthyridines in these reactions. Also, in the reaction of the 2-halogeno-1,X-naphthyridines no evidence for these 2,3-didehydro intermediates was obtained.

a. 3,4-Didehydro-1,5-naphthyridines. Reaction of 3-bromo-1,5-naphthyridine (67) with potassium amide in liquid ammonia gives in high yield a mixture of 3-amino- (69) and 4-amino-1,5-naphthyridine (49) (86:14).²²



⁴⁵ H. J. den Hertog and D. J. Buurman, *Recl. Trav. Chim. Pays-Bas* **86**, 187 (1967).

⁴⁶ G. M. Sanders, M. van Dijk, and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas* **93**, 198 (1974).

⁴⁷ G. M. Sanders, M. van Dijk, and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas* **93**, 273 (1974).

⁴⁸ W. Czuba and M. Woźniak, *Recl. Trav. Chim. Pays-Bas* **93**, 143 (1974).

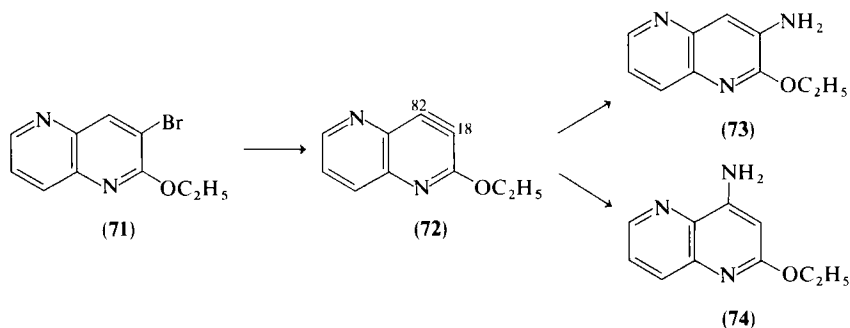
⁴⁹ M. Woźniak, W. Czuba, and H. C. van der Plas, *Roczn. Chem.* **50**, 451 (1976).

⁵⁰ Y. Hamada, M. Sato, and I. Takeuchi, *Yakugaku Zasshi*, **95** 1492 (1975).

These results combined with those obtained in the aminations of the 3-halogenoquinolines (Section III,B,1) show that 3,4-didehydro-1,5-naphthyridine (**68**) is an intermediate and that 2,3-didehydro-1,5-naphthyridine does not occur, because if it had, then 2-amino-1,5-naphthyridine should have been formed. 4-Bromo-1,5-naphthyridine (**70**) also gives a mixture of **69** and **49**. The ratio is 77:23, which indicates that the 4-bromo compound (**70**) undergoes $S_N(AE)^{ipso}$ aminodebromination to **49**²² in addition to an $S_N(EA)$ process via **68**, yielding **49** as well as **69**.

The addition ratio in **68** (86:14) is very different from the ratio of addition of the amide ion to C-3 and C-4 in 3,4-didehydroquinoline (**63**) (45:55). The less favored addition to C-4 in **68** is probably due to a hindered attack of the amide ion at C-4 because of the Coulomb electron repulsion between the negatively charged incoming amide ion and the sp^2 electron pair of the nitrogen at position 5.

It has been reported that 3-bromo-2-ethoxy-1,5-naphthyridine (**71**) with potassium amide gives as sole product the unrearranged 3-amino-2-ethoxy-



1,5-naphthyridine (**73**).²² This result is surprising because both 3-bromo-2-ethoxypyridine⁵¹ and 3-bromo-2-ethoxyquinoline⁵² give the respective 4-amino-2-ethoxy compounds as the main products. Later investigations have shown, however, that the compound originally assigned as 3-bromo-2-ethoxy-1,5-naphthyridine is in fact the isomeric 3-bromo-1-ethyl-1,5-naphthyridin-2[1*H*]-one (**78**).⁵³ Furthermore, 3-bromo-2-ethoxy-1,5-naphthyridine (**71**), prepared by an unambiguous, independent method, was found to give with potassium amide a mixture of 3- and 4-amino-2-ethoxy-1,5-naphthyridine (**73** and **74**) (18:82).⁵³ The formation of both aminoethoxy compounds clearly points to 3,4-didehydro-2-ethoxy-1,5-naphthyridine (**72**) as intermediate. In **72** the ethoxy group with its strongly meta-directing

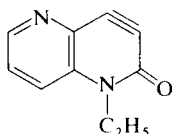
⁵¹ H. J. den Hertog, M. J. Pieterse, and D. J. Buurman, *Recl. Trav. Chim. Pays-Bas* **82**, 1173 (1963).

⁵² J. Pomorski, H. J. den Hertog, D. J. Buurman, and N. H. Bakker, *Recl. Trav. Chim. Pays-Bas* **92**, 970 (1973).

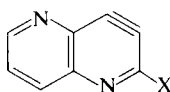
⁵³ H. J. W. van den Haak and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **99**, 83 (1980).

power⁴⁴ surpasses the directive influence of the ring nitrogen, making addition at position 4 more favorable.

Convincing evidence has also been presented for the formation of the intermediate 3,4-didehydro-1-ethyl-1,5-naphthyridin-2[1*H*]-one (75),^{5,3} of the anion of 2-amino-3,4-didehydro-1,5-naphthyridine (76)^{5,2} and of 2-bromo-3,4-didehydro-1,5-naphthyridine (77).^{5,2}

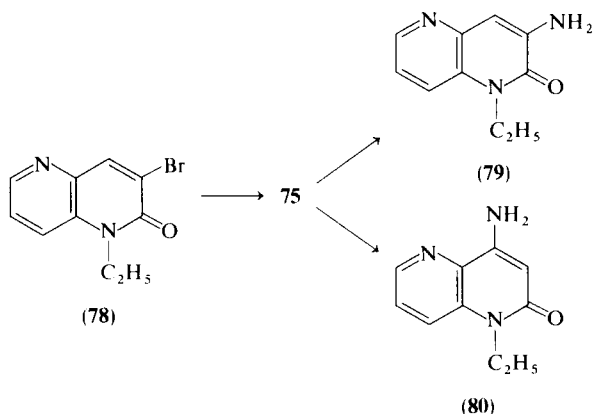


(75)

(76) X = NH⁻

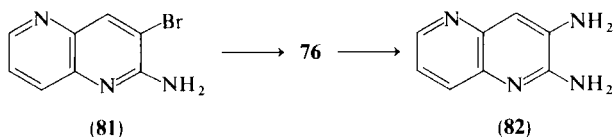
(77) X = Br

3-Bromo-1-ethyl-1,5-naphthyridin-2[1*H*]-one (78) with potassium amide gives a mixture of 3- and 4-amino-1-ethyl-1,5-naphthyridin-2[1*H*]-one (79: 13% and 80: 58%).^{5,3} As intermediate species 75 is proposed in which the



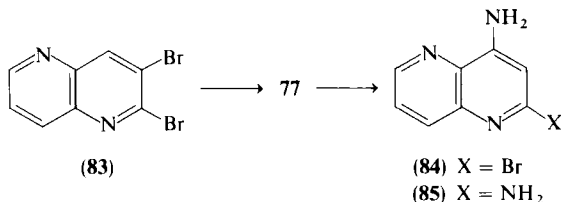
position of addition of the amide ion is governed by the inductive effect of the electron-attraction ($-I$) of the "carboxamido group," which favors attack of the amide ion to C-4.

Reaction of 2-amino-3-bromo-1,5-naphthyridine (81) with potassium amide gives 2,3-diamino-1,5-naphthyridine (82), the formation of which can be explained by a site-specific addition of the amide ion to C-3 in the anionic intermediate (76).^{5,2} This addition pattern is very similar to the one observed



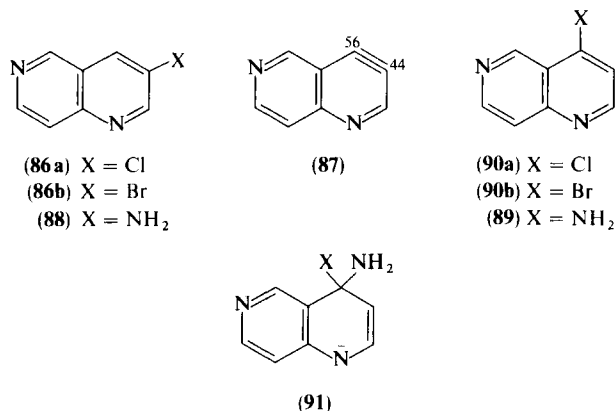
in the anions of 2-amino-3,4-didehydroquinoline⁵⁴ and 2-amino-3,4-didehydropyridine.⁵⁵

2-Bromo-3,4-didehydro-1,5-naphthyridine (**77**) is suggested as an intermediary species in the formation of 2,4-diamino-1,5-naphthyridine (**85**: 80%) from 2,3-dibromo-1,5-naphthyridine (**83**) and potassium amide.⁵² The



2,4-diamino compound (**85**) has as its precursor 4-amino-2-bromo-1,5-naphthyridine (**84**) formed by addition of the amide ion to the 3,4-didehydro compound (**77**). Compound **84** reacts further to produce **85** in an S_N(AE)^{ipso} process.

b. 3,4-Didehydro-1,6-naphthyridines. Reaction of 3-bromo-1,6-naphthyridine (**86b**) with potassium amide in liquid ammonia gives a mixture of 3- and 4-amino-1,6-naphthyridine (**88** and **89**)⁴⁸. No trace of 2-amino-1,6-naphthyridine (**51**) could be detected. These results suggest the intermediacy



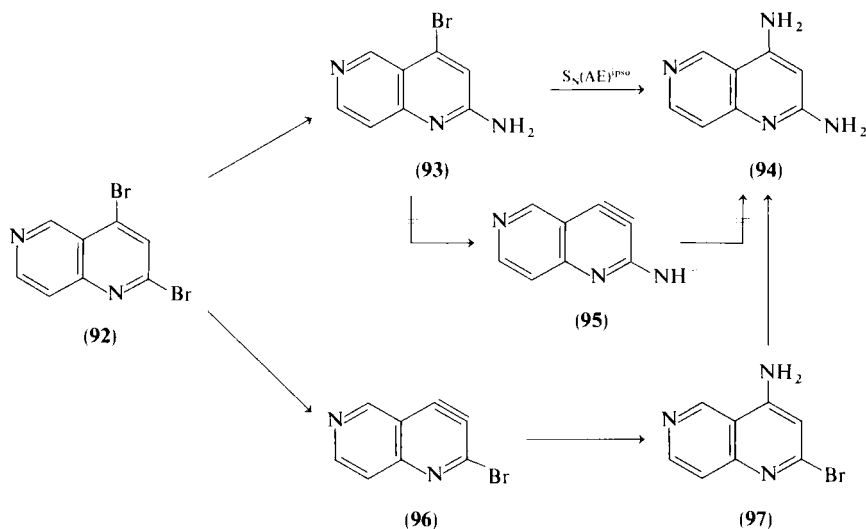
of 3,4-didehydro-1,6-naphthyridine (**87**) in this reaction. Measurement of the amino compounds **88** and **89** in the crude reaction mixture by ¹H-NMR spectroscopy gives the accurate addition ratio of 44:56.²⁹ This ratio is nearly equal to the one found⁴⁵ for 3,4-didehydroquinoline (**63**), and it suggests that

⁵⁴ H. J. den Hertog and D. J. Buurman, *Recl. Trav. Chim. Pays-Bas* **91**, 841 (1972).

⁵⁵ J. W. Streif and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas* **85**, 803 (1966).

86b undergoes only an $S_N(EA)$ process. The reactions of 3-chloro-, 4-chloro-, and 4-bromo-1,6-naphthyridine (**86a**, **90a**, and **90b**, respectively) with potassium amide also give a mixture of **88** and **89**.⁴⁸ Thus, in all three reactions **87** plays a role as intermediate. The ratios of amino products obtained in these three reactions, determined by weighing each of the amino compounds after isolation by TLC, differ strongly (**88**:**89**) is 43:57 for 4-bromo, 77:23 for 3-chloro, and 61:49 for 4-chloro). A more direct method for determining the ratio of amino products, such as $^1\text{H-NMR}$ spectroscopy of the crude reaction mixture (see above), may provide us with more accurate values for these addition ratios. Therefore it would be of interest to reinvestigate these reactions to establish if the addition ratio is really independent of the nature of the halogen atom at C-3 and to determine the contribution of the $S_N(AE)$ process in the amination of the 4-halogeno-1,6-naphthyridines involving **91**.

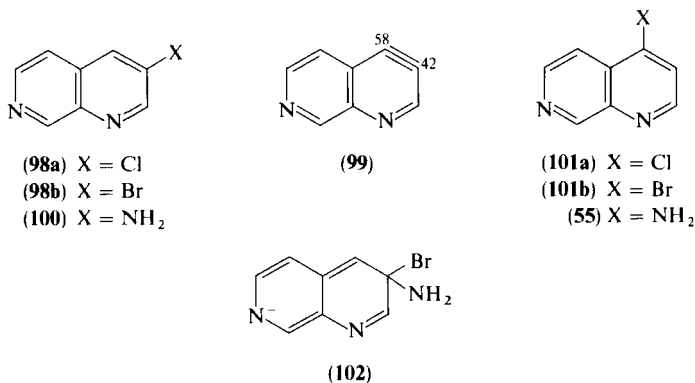
2,4-Diamino-1,6-naphthyridine (**94**) was formed on reaction of 2,4-dibromo-1,6-naphthyridine (**92**) with KNH_2/NH_3 .⁵⁶ The intermediacy of



the 3,4-didehydro compound (**95**) was postulated. This seems unlikely because it is known that the anionic amino group has a strong ortho-directing power.^{52,54,55} It seems more reasonable to advance that **94** was formed either in an $S_N(AE)^{\text{ipso}}$ process from **93** or via 2-bromo-3,4-didehydro-1,6-naphthyridine (**96**) and 4-amino-2-bromo-1,6-naphthyridine (**97**).

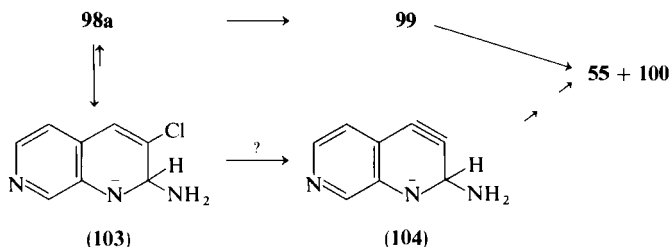
c. *3,4-Didehydro-1,7-naphthyridine*. 3-Amino- and 4-amino-1,7-naphthyridine (**100** and **55**) are obtained on amination of both 3-bromo- (**98b**) and 3-chloro-1,7-naphthyridine (**98a**) with potassium amide in liquid

⁵⁶ W. Czuba, T. Kowalska, and P. Kowalski, *Pol. J. Chem.* **52**, 2369 (1978).



ammonia at -33°C for 4 h.²⁶ No evidence for the presence of the 2-amino-1,7-naphthyridine (**53**) was found. The rate of the amination is higher for the bromo compound than for the chloro, but the ratio in which the two amino compounds are formed (**100**:**55** = 42:58) is independent of the nature of the halogen atom. This is good evidence for the intermediacy of 3,4-didehydro-1,7-naphthyridine (**99**). The addition ratio of the amide ion to C-3 and C-4 is nearly the same as that in 3,4-didehydroquinoline (**63**) (44:56).⁴⁵ Apparently, the presence of the nitrogen atom at position 7 has no influence on the addition pattern and seems to exclude a notable contribution of an addition-elimination reaction involving σ -adduct **102**.

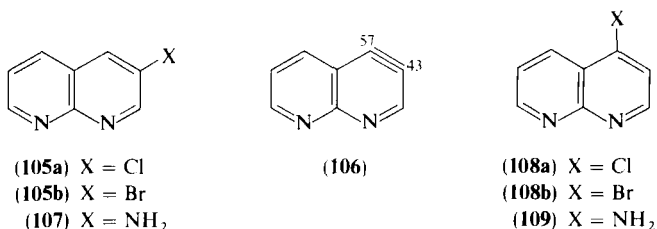
On dissolving 3-chloro-1,7-naphthyridine (**98a**) in liquid ammonia containing potassium amide unambiguous ¹H-NMR evidence for the formation of the σ -adduct 2-amino-3-chloro-1,2-didehydro-1,7-naphthyridinide (**103**) has been obtained²⁶ (Section II,B,1). Apparently σ -adduct formation at C-2 in **98a** precedes the formation of the 3,4-didehydro compound (**99**). This



interesting ¹H-NMR result raises the question of whether the mixture of amino compounds **100** and **55** is formed by dehydrochlorination of the σ -adduct (**103**) into 2-amino-1,2-dihydro-3,4-didehydro-1,7-naphthyridinide (**104**), followed by an amide addition to C-3 and C-4, or whether it is formed directly from **99**.

When reacting the 4-X-1,7-naphthyridines (**101a** and **101b**) with potassium amide in liquid ammonia at -33°C for 4 h, a mixture of **100** and **55** was again obtained.⁴⁹ This result justifies the conclusion that in these reactions **99** is again intermediate. However, the ratio in which both amino compounds are formed is strongly dependent on the nature of the halogen atom at position 4: for X = 4-chloro, **100**:**55** = 22:78 and for X = 4-bromo, **100**:**55** = 35:65. Since these addition ratios are different from the one observed²⁶ in the reaction of 3-bromo compound **98b** (42:58), it is evident that in the amination of **101a** and **101b** the addition-elimination [$\text{S}_{\text{N}}(\text{AE})$] process also is operative. On the basis of the data available, and taking into account their accuracy, it can be calculated that about 20–30% of **101b** reacts according to this $\text{S}_{\text{N}}(\text{AE})$ process.

d. 3,4-Didehydro-1,8-naphthyridine. Evidence has been presented²⁹ for the occurrence of 3,4-didehydro-1,8-naphthyridine (**106**) in the reaction of 3-bromo- (**105b**) and 3-chloro-1,8-naphthyridine (**105a**) with potassium amide in liquid ammonia. In both reactions a mixture of 3- and 4-amino-



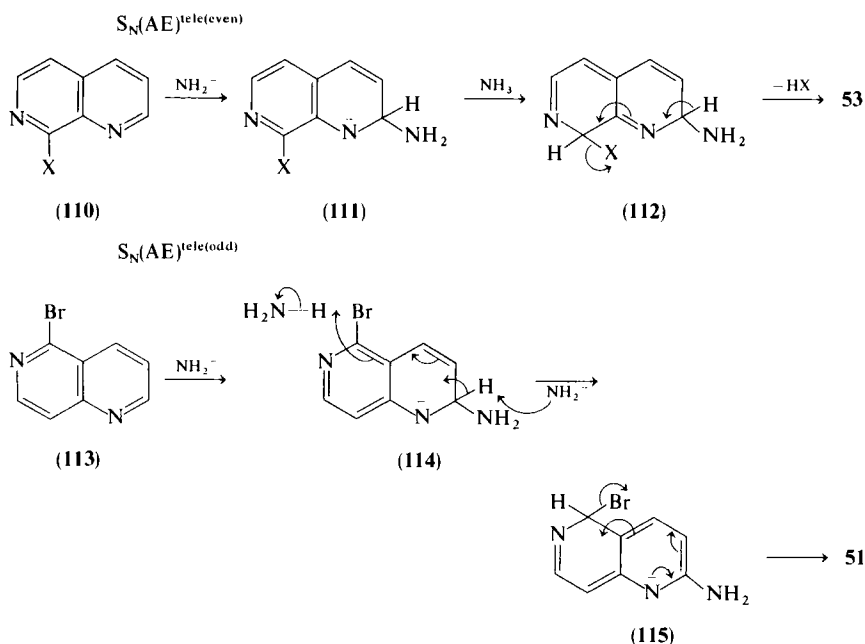
1,8-naphthyridine (**107** and **109**) was obtained. No trace of a 2-amino compound was found. The ratio of **107** and **109** determined by quantitative ^1H -NMR spectroscopy of the crude reaction mixture was 43:57 when the 3-bromo compound was used as substrate and 33:66 when the 3-chloro compound was used. Because much higher yields of amino compounds were obtained with **105b** than with **105a**—in the latter case many highly colored and tarry substances are formed—the ratio of **107**:**109** obtained from **105b** was considered to be the more reliable one. It is of interest to note that this ratio is nearly the same as the addition ratio C-3:C-4 in 3,4-didehydroquinoline (**63**),⁴⁵ 3,4-didehydro-1,6-naphthyridine (**87**),^{29,48} and 3,4-didehydro-1,7-naphthyridine (**99**).^{49,26} The similarity proves that the presence of nitrogen at positions 6, 7, and 8 in the 1,X-naphthyridines barely influences the addition ratio in the 3,4-didehydropyridine ring.

It has been reported that **105a** gives an adduct (**32**) at C-2²⁹ (see Section II,B,1). Therefore, it can be questioned (in analogy to the reaction of 3-chloro-1,7-naphthyridine [**98a**]) whether amino products **107** and **109** are formed via **106** or by dehydrohalogenation of **32**, followed by addition of ammonia.

Amination of 4-bromo- and 4-chloro-1,8-naphthyridine (**108a** and **108b**) also affords a mixture of **107** and **109** (ratio of about 30:70 determined by $^1\text{H-NMR}$ spectroscopy of the crude reaction mixture).²⁹ This ratio is somewhat different from that found in the amination of **105b** (43:57) and indicates that **108** undergoes an aminodebromination at C-4 [$\text{S}_{\text{N}}(\text{AE})^{\text{ipso}}$], in addition to the $\text{S}_{\text{N}}(\text{EA})$ reaction involving the intermediacy of **106**. It was calculated that 4-bromo-1,8-naphthyridine reacts at about 40% according to this $\text{S}_{\text{N}}(\text{AE})$ process and 60% according to the $\text{S}_{\text{N}}(\text{EA})$ mechanism.²⁹

2. Amino Dehalogenations Involving Tele Substitutions

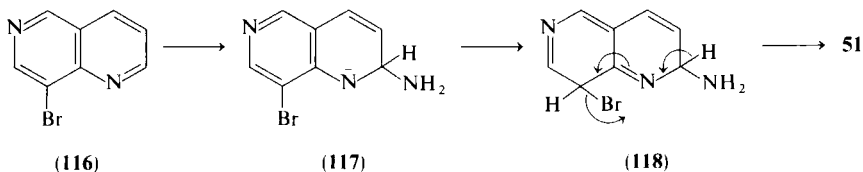
An interesting feature of the reactivity of halogenonaphthyridines toward nucleophiles is their readiness to undergo tele substitutions. Potassium amide in liquid ammonia is an appropriate reagent. As indicated in Section III,B, in tele substitutions the nucleophile enters a site more than one position removed from the one that is left by the leaving group. In the tele substitutions two different pathways can be discerned, even or odd, depending on whether there is an even or odd number of atoms present between the position of nucleophilic attack and the position of the leaving group. They are illustrated by the two following examples:



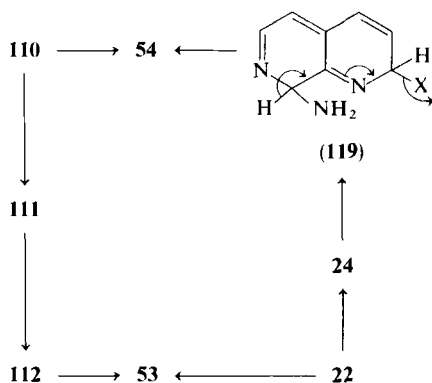
8-Chloro-1,7-naphthyridine (**110**: X = Cl) gives on amination with KNH_2/NH_3 the tele product 2-amino-1,7-naphthyridine (**53**) in addition to the ipso product 8-amino-1,7-naphthyridine (**54**).^{10,25} The formation of **53** involves as intermediates anionic σ -adduct **111** (X = Cl) (its existence has been proved by NMR spectroscopy; see Section II,B,1) and probably 2-amino-2,8-dihydro-8-chloro-1,7-naphthyridine (**112**). The latter undergoes a base-catalyzed dehydrochlorination, yielding **53**. Because there are four atoms between position 2 and 8, the reaction is called an even tele substitution.

Amination of 5-bromo-1,6-naphthyridine (**113**) gives as tele product 2-amino-1,6-naphthyridine (**51**),²⁴ but in addition to the intermediacy of anionic σ -adduct (**114**) (as proved by ^1H -NMR spectroscopy), its formation involves anionic σ -adduct **115**, which is formed by a proton shift from **114**. The number of atoms between positions 2 and 5 is five, thus this reaction is referred to as an odd tele substitution. Both types of tele substitution involve Addition of the nucleophile as the initial step and Elimination of the leaving group as the last step. However, in the even tele substitution the elimination can be described to take place from a neutral dihydro species, while in the odd tele substitution the elimination must occur from an anionic intermediate. In the naphthyridines several examples of even and odd tele substitutions are found, and in the following sections the results of studies concerned with tele amination are presented.

a. *Even Tele Substitutions.* Treatment of 8-bromo-1,6-naphthyridine (**116**) with potassium amide in liquid ammonia gives the tele product 2-amino-1,6-naphthyridine (**51**). Intermediates in the tele reaction are the anionic σ -adduct (**117**) whose existence has been proved by NMR spectroscopy (Section II,B,1) and 2-amino-8-bromo-2,8-dihydro-1,6-naphthyridine (**118**) formed by protonation of **117**.

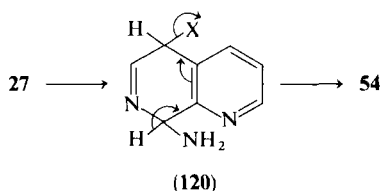


If the halogeno atom is α or γ to the ring nitrogen, competition between an $\text{S}_{\text{N}}(\text{AE})^{\text{ipso}}$ and an $\text{S}_{\text{N}}(\text{AE})^{\text{tele}}$ pathway can occur. This is demonstrated in the amination of 8-X-1,7-naphthyridine (**110**: X = Cl, Br),^{10,25} providing in small yields (10–15%) both the ipso product (**54**) and the tele product (**53**) (Section III,B,2). The ratio tele:ipso (R) is dependent on the nature of the halogen atom (R = 0.8 for X = Cl and 0.5 for X = Br). Tele amination has



also been found²⁵ in the amination of 2-X-1,7-naphthyridine (22: X = Cl, Br), yielding 8-amino-1,7-naphthyridine (54). Intermediates are the anionic σ -adduct (24) and the 2,8-dihydro compound (119). The ratio tele:ipso is about 0.55 for X = Cl and about 14 for X = Br.

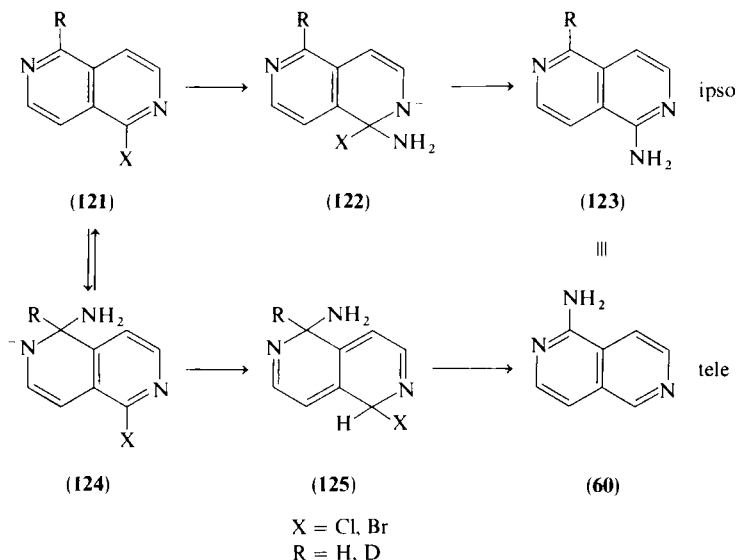
One example has been reported of the occurrence of an even tele substitution within one ring of the 1,7-naphthyridine system. Amination of 5-halogeno-1,7-naphthyridines (27) with potassium amide gave 8-amino-1,7-naphthyridine (54).²⁸ This reaction bears a close analogy to the formation



of 1-aminoisoquinoline from 4-halogenoisoquinoline⁴⁷ and involves the 8-amino-5-X-5,8-dihydro-1,7-naphthyridine (120) as an intermediate.

Tele substitutions that occur with the halogen derivatives of naphthyridines, which are characterized by a high degree of symmetry, cannot simply be recognized by the structure of the products obtained. For example, the amination of 1-halogeno-2,6-naphthyridines (121, R = H) yields 1-amino-2,6-naphthyridine (123: R = H) (5-amino-2,6-naphthyridine 60).²¹ It is evident that this compound can be formed either by an $S_N(AE)^{ipso}$ or $S_N(AE)^{tele}$ pathway or by both mechanisms.

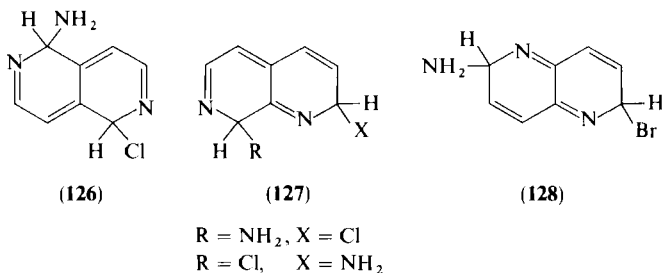
There is sound NMR evidence²¹ that a solution of the 1-chloro and 1-bromo compound (121: R = H) in liquid ammonia (containing potassium amide) contains the 5-amino σ -adduct (124: R = H) (Section II,B,1). This



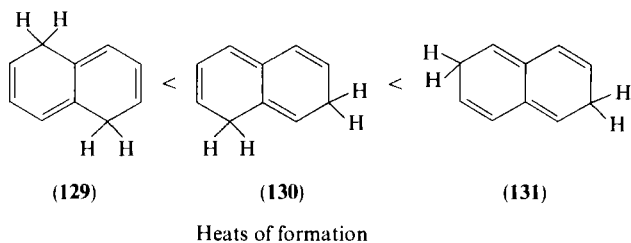
indicates that the first step in the $S_N(AE)^{tele}$ process certainly occurs. More convincing evidence for occurrence of the tele process was obtained by study of the amination of 1-chloro-5-deutero-2,6-naphthyridine (**121**: X = Cl, R = D). It is clear from the scheme above that if the amino dehalogenation occurs according to an $S_N(AE)^{ipso}$ process, then the 1-amino compound (**123**: R = D) contains the same percentage of deuterium labeling at C-5 as was present in the starting material, whereas in an $S_N(AE)^{tele}$ process, no deuterium can be present in the amino compound (**60**) formed. It was found²¹ that after amination of **121** (X = Cl, R = D) the amino compound has a percentage of deuterium that was considerably lower than that present in the starting material.

From the mass spectrometric data it was calculated that the 5-deutero-1-chloro compound reacted about 5 times faster in the $S_N(AE)^{tele}$ process than in the $S_N(AE)^{ipso}$ process. The $S_N(AE)^{tele}$ reaction was found to have a kinetic isotope effect of 2.5. This leads to the conclusion that for the undeuterated 1-chloro-2,6-naphthyridine (**121**: X = Cl, R = H), the $S_N(AE)^{tele}$ substitution proceeds about 13 times faster than does the $S_N(AE)^{ipso}$ process, i.e., 93% of the 1-amino-2,6-naphthyridine is formed in an $S_N(AE)^{tele}$ process. Similar results were obtained with the 1-bromo-2,6-naphthyridine, although the contribution of the $S_N(AE)^{tele}$ process in that substitution reaction was somewhat less important.

Comparison of the tele:ipso ratios in the reactions of 2-chloro-1,7-naphthyridine²⁵ (about 0.6), 8-chloro-1,7-naphthyridine^{10,25} (about 0.8), and 1-chloro-2,6-naphthyridine²¹ (about 13) leads to the conclusion that the 1-chloro-2,6-naphthyridines are much more inclined to undergo the tele substitution than are the isomeric 2- and 8-chloro-1,7-naphthyridines. The variety in reactivity of halogenonaphthyridines to undergo even tele substitutions has some relationship to the thermodynamic stabilities of the dihydro intermediates.²¹ Considering the structure of dihydro intermediates **126** and **127**, it seems likely that the linear-conjugated 1,5-dihydro-2,6-



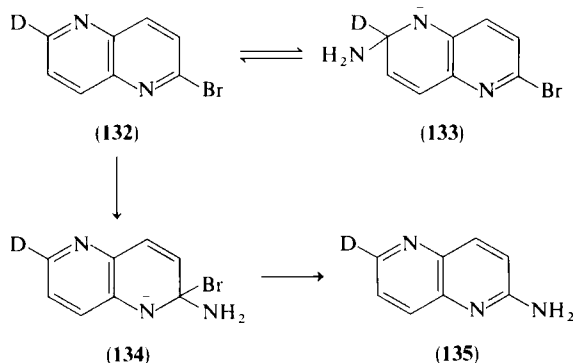
naphthyridine (**126**) is somewhat more stable than the cross-conjugated 2,8-dihydro-1,7-naphthyridine (**127**). Some support for this explanation can be taken from the fact that the estimated heat of formation of cross-conjugated 1,7-(or 2,8-) dihydronaphthalene (**130**) is about 1.4 kJ/mol higher than that of its linear-conjugated 1,5-isomer (**129**).⁵⁷ Estimations of the stability of



2,6-dihydronaphthalene (**131**) indicate that this dihydro compound is about 10 kJ/mol less stable than its 1,5-isomer. On the basis of these data, the prediction can be made that an even tele substitution involving a 2,6-dihydro-naphthyridine (e.g., **128**) as intermediate, would be an unfavorable process. This has indeed been found.²¹ Although a solution of 2-bromo-6-deutero-

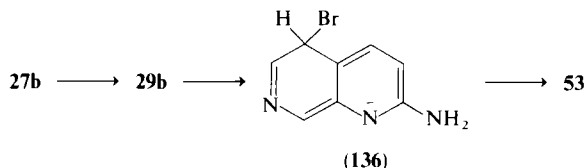
⁵⁷ K. Shaw, D. M. Golden, and S. W. Benson, *J. Phys. Chem.* **81**, 1716 (1977).

1,5-naphthyridine (**132**) in liquid ammonia containing potassium amide provides convincing evidence for the formation of the 1:1 6-amino σ -adduct

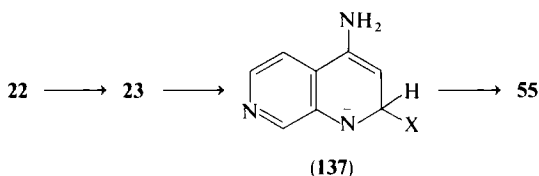


(133), the amino product **(135)** obtained in the amination has the same percentage of deuterium as was present in the starting material. Thus, an $S_N(AE)^{tele}$ process can be excluded and only an $S_N(AE)^{ipso}$ process involving **134** as intermediate occurs.²¹

b. *Odd Tele Substitutions.* There are only a few reactions reported in which halogenonaphthyridines react in odd tele substitutions. An easily recognized odd tele substitution is already mentioned in Section III,B,2 concerning the conversion of 5-bromo-1,6-naphthyridine (**113**) into 2-amino-1,6-naphthyridine (**51**).²⁴ Furthermore, it has been found that amination of 5-bromo-1,7-naphthyridine (**27b**) yields, among other products, 2-amino-1,7-naphthyridine (**53**).²⁸ This tele reaction involves two anionic σ -adducts,



29b and **136**. Product **53** is not formed on amination of 5-chloro-1,7-naphthyridine.²⁸ The 2-halogeno-1,7-naphthyridines (**22**) with potassium amide in liquid ammonia yield a small amount of the odd tele product 4-amino-1,7-naphthyridine (**55**), in addition to the even tele product 8-amino-1,7-naphthyridine (**54**)²⁵ (see Section III,B,2,a) and the ipso product

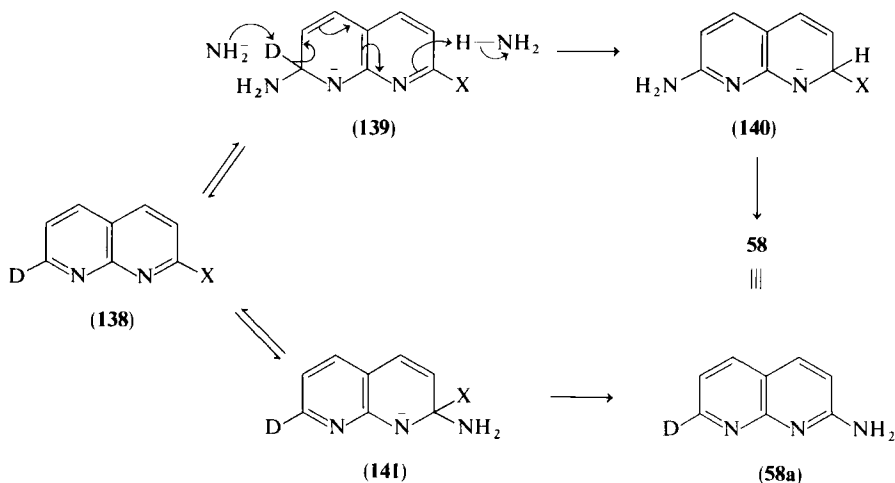


2-amino-1,7-naphthyridine (**53**). The presence of σ -adduct **23**, one of the precursors of **55**, is soundly proved by NMR spectroscopy (Section II,B,1).

An odd tele substitution also occurring in one ring has been observed on amination of 2-bromo-1,5-naphthyridine, yielding 4-amino-1,5-naphthyridine.²¹

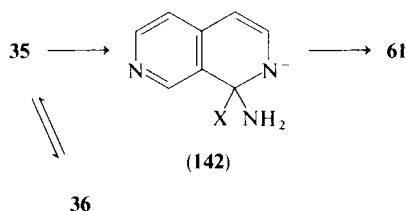
An interesting case of an odd tele substitution has been found when aminating 2-X-1,8-naphthyridine ($X = \text{Cl}, \text{Br}$) with liquid ammonia containing potassium amide.^{10,29,30} The product obtained in the amination was 2-(or 7-) amino-1,8-naphthyridine (**58**). However, carrying out the amination with 2-X-7-deutero-1,8-naphthyridine (**138**), the 2-amino product had a deuterium content considerably less than was present in the starting material. From the amount of deuterium present in the 2-amino compound, it was calculated that for $X = \text{Br}$, 45% of the amino compound was formed according to the $S_N(\text{AE})^{\text{tele}}$ process and that for $X = \text{Cl}$, this percentage was considerably lower (10%).⁵⁸

There is convincing NMR evidence (Section II,B,1) for the presence of the 7-amino σ -adduct (**139**) in the potassium amide/liquid ammonia system.



⁵⁸ Originally it was stated that the formation of 2-bromo-1,8-naphthyridine from 8-bromo-1,8-naphthyridine occurred for 27% *via* the $S_N(\text{AE})^{\text{tele}}$ mechanism.^{10,29} However, when the isotope effect—calculated from the deuterium enrichment in the recovered starting material—was taken into consideration, 45% of telesubstitution was found.^{21,24}

This adduct can react further in the tele reaction to **58** (via the intermediary anion **140**) or can rearrange via **138** into the ipso adduct (**141**). This adduct gives the 2-amino compound (**58a**), having all the deuterium present at C-7. On amination of 1-halogeno-2,7-naphthyridine (**35**) 1-amino-2,7-naphthyridine (**61**) is formed.³⁰ This product could be formed in an odd tele substitution; however, this is not the case despite the fact that **35** gives an exclusive addition of the amide ion at position 8, yielding **36**. With selectively deuterium-labeled 1-halogeno-2,7-naphthyridine evidence has been obtained that the 1-amino compound is exclusively formed in an $S_N(AE)^{ipso}$ process. Apparently, adduct **36**, which is in equilibrium with **35**, rearranges via **35** into the ipso adduct (**142**).



3. Amino Dehalogenations Involving Ipso Substitutions

In many of the reactions already discussed, it has been shown that with potassium amide/liquid ammonia the ipso substitution is competitive with tele substitution and/or didehydronaphthyridine formation and, as discussed in Section IV, with ring transformation reactions. This strong basic and nucleophilic reagent is able to react multifunctionally, leading to competitive reactions. In the absence of potassium amide the reactions are usually less complicated. In this section we deal with reactions in which halogenonaphthyridines exclusively undergo ipso substitution with ammonia. The general picture of the mechanisms of these amino dehalogenations involves an addition of ammonia to the carbon attached to the leaving group, followed by loss of the leaving group. If these reactions are carried out with halogenonaphthyridines, in which the halogen is present in the α - or γ -position to the nitrogen, two methods are usually applied: (1) heating the halogenonaphthyridine with an ethanolic or methanolic solution of ammonia in an autoclave or sealed tube, or (2) passing gaseous ammonia through a solution of halogenonaphthyridine in phenol at higher temperatures. If the halogeno atom is present in a position deactivated for nucleophilic displacement, then the use of $Cu^{II}SO_4$ is necessary. The results of these studies are summarized in Table VII. For convenience the melting points of these rather simple naphthyridines are included.

TABLE VII
 AMINATION OF HALOGENONAPHTHYRIDINES WITH AMMONIA

Substrate	Reagents and reaction conditions	Product	Yield (%)	Melting point (°C)	References
2-Chloro-1,5-naphthyridine	NH ₃ /phenol, acetamide, 190°C, 3 h	2-Amino-1,5-naphthyridine	40 (crude)	206–208	41
3-Bromo-1,5-naphthyridine	NH ₃ /H ₂ O, CuSO ₄ , 170°C, 40 h	3-Amino-1,5-naphthyridine	75	144–145 148–149	59 62
4-Chloro-1,5-naphthyridine	NH ₃ /phenol, acetamide, 170°C, 6 h	4-Amino-1,5-naphthyridine	86	203.5–204.5 202–203	41 60
3-Bromo-1,6-naphthyridine	NH ₃ /H ₂ O, CuSO ₄ , 160°C, 40 h or 170°C, 30 h	3-Amino-1,6-naphthyridine	26 53	223–224 222–224	61 48
4-Chloro-1,6-naphthyridine	NH ₃ /phenol, 160°C, 1 h or 160°C, 6 h	4-Amino-1,6-naphthyridine	20 76	254 248–250	62 48
5-Chloro-1,6-naphthyridine	NH ₃ /phenol, 160°C, 1 h	5-Amino-1,6-naphthyridine	39	204–206	61
8-Bromo-1,6-naphthyridine	NH ₃ /H ₂ O, CuSO ₄ , 180°C, 39 h	8-Amino-1,6-naphthyridine	16.5	135–137	61
2-Chloro-1,7-naphthyridine	NH ₃ /phenol, 170°C, 5 h	2-Amino-1,7-naphthyridine	51	236–238	63
4-Chloro-1,7-naphthyridine	NH ₃ /phenol, 170°C, 6 h	4-Amino-1,7-naphthyridine	52	259–260	49
2-Chloro-1,8-naphthyridine	NH ₃ /phenol, 170–175°C, 5 h	2-Amino-1,8-naphthyridine	66	143–144	64
	NH ₃ /EtOH, 150°C, 3 h		83	141–142	65
3-Bromo-1,8-naphthyridine	NH ₃ /H ₂ O, CuSO ₄ , 160°C, 16–20 h	3-Amino-1,8-naphthyridine	49	142–144	29,66
4-Bromo-1,8-naphthyridine	NH ₃ /phenol, 170–170°C, 6 h	4-Amino-1,8-naphthyridine	75	185–187	67
1-Chloro-2,6-naphthyridine	NH ₃ /phenol, 175°C, 6 h	1-Amino-2,6-naphthyridine	58	243–244	20
<i>Substituted halogenonaphthyridines</i>					
2-Chloro-3-carboxyamido-1,5-naphthyridine	NH ₃ , 140°C	2-Amino-3-carboxyamido-1,5-naphthyridine	<i>b</i>	<i>b</i>	68
4-Anilino-2-chloro-1,5-naphthyridine	NH ₃ /EtOH, 170°C, 80 h	2-Amino-4-anilino-1,5-naphthyridine	61	152	69
3-Bromo-1-ethyl-1,5-naphthyridin-2[1 <i>H</i>]-one ^a	NH ₃ /H ₂ O, CuSO ₄ , 170°C, 45 h	3-Amino-1-ethyl-1,5-naphthyridin-2[1 <i>H</i>]-one ^a	89	200–202	22,53
2-Chloro-3-nitro-1,5-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	2-Amino-3-nitro-1,5-naphthyridine	67	254–255	27
4-Chloro-3-nitro-1,5-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	4-Amino-3-nitro-1,5-naphthyridine	75	228–229	70
2-Chloro-3-nitro-1,6-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	2-Amino-3-nitro-1,6-naphthyridine	75	262	27
4-Chloro-3-nitro-1,6-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	4-Amino-3-nitro-1,6-naphthyridine	89	298–299	70

TABLE VII (Continued)

Substrate	Reagents and reaction conditions	Product	Yield (%)	Melting point (°C)	References
8-Chloro-5-nitro-1,7-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	8-Amino-5-nitro-1,7-naphthyridine	61	247–248	70
2-Chloro-3-nitro-1,8-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	2-Amino-3-nitro-1,8-naphthyridine	70	276–277	70
4-Chloro-3-nitro-1,8-naphthyridine	NH ₃ /EtOH, 110°C, 4 h	4-Amino-3-nitro-1,8-naphthyridine	56	> 350	71
2-Chloro-3-phenyl-1,8-naphthyridine-7[8H]-one	NH ₃ /EtOH, 150°C, 48 h	2-Amino-3-phenyl-1,8-naphthyridine-7[8H]-one	45	306–308	72
2-Chloro-4-phenyl-1,8-naphthyridine-7[8H]-one	NH ₃ /EtOH, 120°C, 80 h	2-Amino-4-phenyl-1,8-naphthyridine-7[8H]-one	79	> 330	73
5-Chloro-2-methyl-1,8-naphthyridine	NH ₃ /phenol, acetamide, 160°C, 1 h	5-Amino-2-methyl-1,8-naphthyridine	84	211–212	79
<i>Dihalogenonaphthyridines</i>					
2,6-Dibromo-1,5-naphthyridine	NH ₃ /H ₂ O, 160°C, 6 h	2-Amino-6-bromo-1,5-naphthyridine	60	211	74
2,6-Dibromo-1,5-naphthyridine	NH ₃ /H ₂ O, 180°C, 8 h	2,6-Diamino-1,5-naphthyridine	62.5	340	74
2,3-Dibromo-1,5-naphthyridine	NH ₃ /EtOH, 160°C, 48 h	2-Amino-3-bromo-1,5-naphthyridine	—	184–186	52
3,4-Dibromo-1,5-naphthyridine	NH ₃ /EtOH, 150°C, 6 h	4-Amino-3-bromo-1,5-naphthyridine	39	131–132	27
3,7-Dibromo-1,5-naphthyridine	NH ₃ /H ₂ O, CuSO ₄ , 170°C, 45 h	3,7-Diamino-1,5-naphthyridine	54	318–320	75
2,4-Dichloro-1,5-naphthyridine	NH ₃ /EtOH, 170°C, 20 h and NH ₃ /H ₂ O, CuSO ₄ , 200°C, 90 h	2-Amino-4-chloro-1,5-naphthyridine	47	184	69
4,8-Dichloro-1,5-naphthyridine	NH ₃ /EtOH, 170–180°C, 10 h	2-Amino-4-hydroxy-1,5-naphthyridine	83	320	69
3,4-Dibromo-1,6-naphthyridine	NH ₃ /EtOH, 130°C, 4 h	4,8-Diamino-1,5-naphthyridine	56	252–255	76
3,4-Dibromo-1,7-naphthyridine	NH ₃ /EtOH, 130°C, 4 h	4-Amino-3-bromo-1,6-naphthyridine	49	294–295	27
3,4-Dibromo-1,8-naphthyridine	NH ₃ /EtOH, 140°C, 12 h	4-Amino-3-bromo-1,7-naphthyridine	80	205–206	27
3,4-Dichloro-1,8-naphthyridine	NH ₃ /EtOH, 140°C, 10 h	4-Amino-3-bromo-1,8-naphthyridine	74	241–243	71
		4-Amino-3-chloro-1,8-naphthyridine	60	225–227	71

^a Structures of these compounds were earlier established as 3-bromo- and 3-amino-2-ethoxy-1,5-naphthyridine.

⁵⁹ W. Czuba, *Recl. Trav. Chim. Pays-Bas* **82**, 988 (1963).

⁶⁰ F. H. Case and J. A. Brennan, *J. Am. Chem. Soc.* **81**, 6297 (1959).

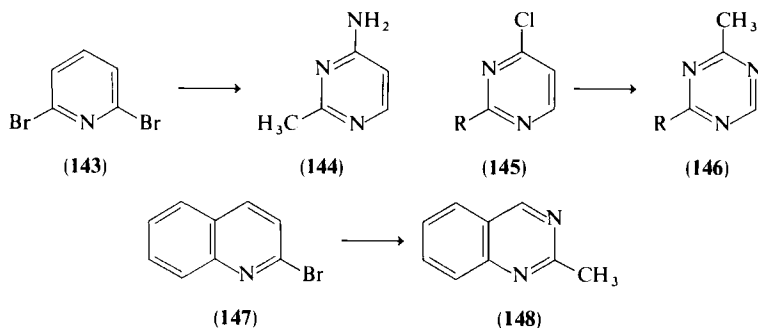
⁶¹ E. V. Brown, S. R. Mitchell, and A. C. Plaszc, *J. Org. Chem.* **40**, 2369 (1975).

⁶² E. V. Brown, A. C. Plaszc, and S. R. Mitchell, *J. Heterocycl. Chem.* **7**, 661 (1970).

⁶³ W. Czuba and M. Woźniak, *Rocz. Chem.* **48**, 1815 (1974).

IV. Ring Transformation of Naphthyridines

Ring transformations were found in numerous reactions of halogeno-naphthyridines with potassium amide in liquid ammonia, in addition to the formation of amino compounds, which involve a Chichibabin adduct (Section II,B,1), the intermediacy of a naphthyridyne (Section III,B,1), a tele σ -adduct (Section III,B,2), or an ipso σ -adduct (Section III,B,3). These ring transformations are often observed as important side reactions, particularly in the reaction of 2-halogeno-1,X-naphthyridines ($X = 5, 6,$ and 7). All these ring transformation reactions are characterized by the fact that the 1,X-naphthyridine ring system is converted into a 1,3,X-triazanaphthalene ring system ($X = 5, 6,$ and 7) containing a methyl group at position 2. This type of ring transformation is quite general in reactions of 1-aza-2-halogenoazines with KNH_2/NH_3 . They show the common feature that the initial adduct formation takes place at the position meta to the leaving group at position 2. This is exemplified in the conversions of 2,6-dibromopyridine (143) to



⁶⁴ W. Roszkiewicz and M. Woźniak, *Synthesis*, 691 (1976).

⁶⁵ M. Woźniak and M. Skibu, *Pol. J. Chem.* **55**, 937 (1981).

⁶⁶ I. Takeuchi, I. Ozawa, T. Ogaki, Y. Hamada, and T. Ito, *Yakugaku Zasshi* **98**, 1279 (1978).

⁶⁷ W. Czuba and M. Woźniak, *Synthesis*, 809 (1974).

⁶⁸ A. Decormeille, G. Queguiner, and P. Pastour, *C. R. Acad. Sci., Ser. C* **280**, C-381 (1975).

⁶⁹ V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 204 (1958).

⁷⁰ M. Woźniak, *Zesz. Nauk. Uniw. Jagiellon., Pr. Chem.* **27**, 33 (1982).

⁷¹ M. Woźniak, *Pol. J. Chem.* **53**, 1665 (1979).

⁷² S. Carboni, A. Da Settimo, P. L. Ferrarini, and P. L. Ciantelli, *J. Heterocycl. Chem.* **7**, 1037 (1970).

⁷³ S. Carboni, A. Da Settimo, P. L. Ferrarini, and I. Tonetti, *Gazz. Chim. Ital.* **97**, 1262 (1967).

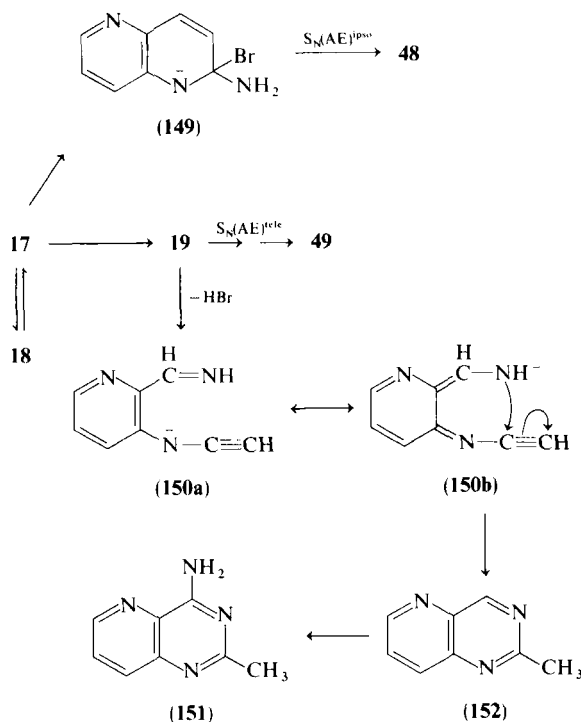
⁷⁴ J. Pomorski and H. J. den Hertog, *Rocz. Chem.* **47**, 549 (1973).

⁷⁵ W. Czuba, *Rocz. Chem.* **39**, 1589 (1963).

⁷⁶ S. B. Brown and M. J. S. Dewar, *J. Org. Chem.* **43**, 1331 (1978).

4-amino-2-methylpyrimidine (**144**),⁷⁷ of 4-chloro-2-R-pyrimidine (**145**) to 2-R-4-methyl-1,3,5-triazine (**146**),⁷⁸ and of 2-bromoquinoline (**14**) to 2-methylquinazoline (**148**).⁴⁵

Reaction of 2-bromo-1,5-naphthyridine (**17**) with KNH_2/NH_3 gives,²² in addition to 2-amino-1,5-naphthyridine (**48**: 77%) formed via **149**, 4-amino-1,5-naphthyridine (**49**: 1%) and product $\text{C}_8\text{H}_8\text{N}_4$, which was later proved to be 4-amino-2-methyl-1,3,5-triazanaphthalene (**151**: 11%).²³ The ring transformation of **17** into **151** is explained by the intermediary formation of C-4



adduct **19**; however, there is no NMR evidence for its existence. On the contrary, the only σ -adduct whose existence has been proved is C-6 adduct **18**.²¹ However, **18** cannot be an intermediate for any of the products formed. Apparently, **19** is partly converted to the tele product (**49**), and part also

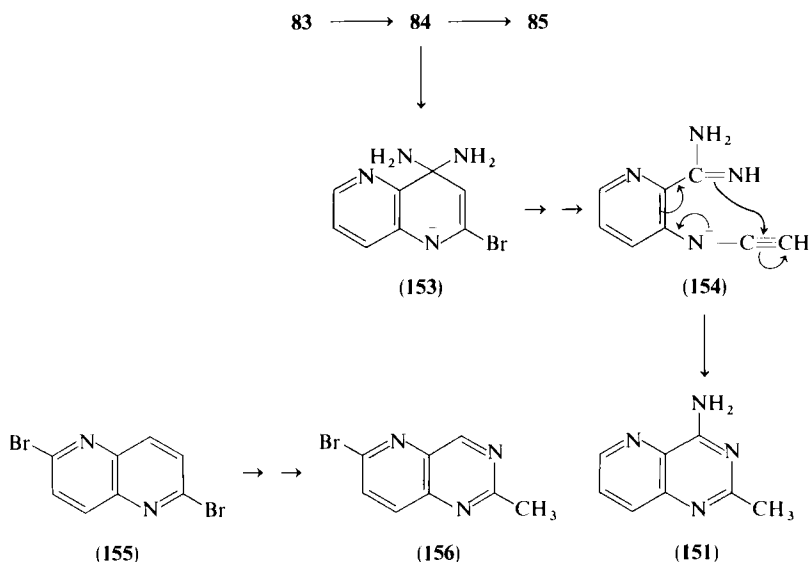
⁷⁷ H. J. den Hertog, H. C. van der Plas, M. J. Pieterse, and J. W. Streef, *Recl. Trav. Chim. Pays-Bas* **84**, 1569 (1965).

⁷⁸ H. W. van Meeteren and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas* **86**, 15 (1967).

⁷⁹ E. V. Brown, *J. Org. Chem.* **30**, 1607 (1965).

undergoes a base-catalyzed 1,4-dehydrobromination leading to bond fission between C-3 and C-4, yielding 3-ethynylamino-2-formiminopyridine (**150a** \leftrightarrow **150b**). After cyclization, 2-methyl-1,3,5-triazanaphthalene (**152**) is obtained, which then can undergo a Chichibabin amination at C-4, yielding **151**. Amination of 2,3-dibromo-1,5-naphthyridine (**83**) with potassium amide in liquid ammonia leads to a mixture of 2,4-diamino-1,5-naphthyridine (**85**) and 4-amino-1,3,5-triazanaphthalene (**151**).⁵²

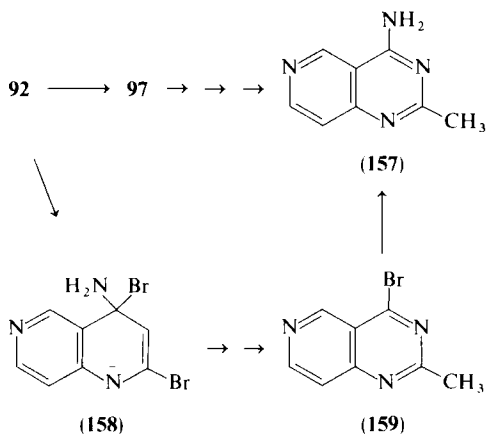
4-Amino-2-bromo-1,5-naphthyridine (**84**) may be an intermediate (see Section III,B,1,a for its formation) that undergoes a covalent amination at C-4, yielding the gem 4,4-diamino-2-bromodihydro-1,5-naphthyridinide (**153**) and an amino debromination at C-2, yielding **85**. Ring opening of **153**



and ring closure via **154** as indicated gives **151**. The addition of an amide ion to a carbon that is substituted by an amino group is not unprecedented. Also 4-amino-2-bromoquinoline has been proposed to undergo a similar addition.⁵⁴

Quite similar to the conversion of **17** and **83** into **151** is the reaction of 2,6-dibromo-1,5-naphthyridine (**155**) with KNH_2/NH_3 , which gives ring transformation into 6-bromo-2-methyl-1,3,5-triazanaphthalene (**156**), as well as 2-amino-6-bromo-1,5-naphthyridine and 2,6-diamino-1,5-naphthyridine.⁷⁴

In the 1,6-naphthyridine series the amide-induced ring transformation of 2,4-dibromo-1,6-naphthyridine (**92**) into 4-bromo-2-methyl-1,3,6-triazanaph-



thalene (159) and 4-amino-2-methyl-1,3,6-triazanaphthalene (157) (as well as 2,4-diamino-1,6-naphthyridine) has been reported.⁵⁶ Whether the 4-amino compound (157) is formed by amino debromination of the 4-bromo compound (159) or from the intermediate 4-amino-2-bromo-1,6-naphthyridine (97) is unsolved. It is evident that the formation of 159 will involve the intermediacy of the 4-amino adduct (158).

It has been reported that 2-bromo(chloro)-1,7-naphthyridine (22) with KNH_2/NH_3 gives 4-amino-2-methyl-1,3,7-triazanaphthalene (162),²⁵ in addition to 2-amino-1,7-naphthyridine (53) and two tele amination products, 4-amino-(55) and 8-amino-1,7-naphthyridine (54).

The formation of all products is summarized in the following scheme and is supported by the fact that the existence of intermediary σ -adducts 23 and 24 are soundly proved by NMR spectroscopy (Section II,B,1).

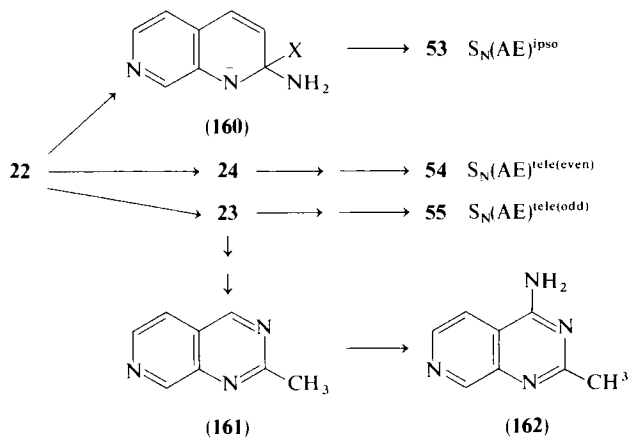


TABLE VIII
SUMMARY OF THE SEVERAL REACTIONS OF CHLORO- AND BROMONAPHTHYRIDINES WITH KNH_2/NH_3

Substrate	Aminoproducts formed by:			Ring transformation into:	References
	$\text{S}_{\text{N}}(\text{AE})^{\text{ipso}}$	$\text{S}_{\text{N}}(\text{AE})^{\text{tele}}$	$\text{S}_{\text{N}}(\text{EA})$		
2-Br-1,5-naphthyridine	2-NH ₂	4-NH ₂	—	4-NH ₂ -2-CH ₃ -1,3,5-triazanaphthalene	21,22
3-Br-1,5-naphthyridine	—	—	3-NH ₂ 4-NH ₂	—	22
4-Br-1,5-naphthyridine	4-NH ₂	—	3-NH ₂ 4-NH ₂	—	22
2,3-DiBr-1,5-naphthyridine	^a	—	^a	4-NH ₂ -2-CH ₃ -1,3,5-triazanaphthalene	52
2,6-DiBr-1,5-naphthyridine	2-NH ₂ -6-Br 2,6-DiNH ₂	—	—	6-Br-2-CH ₃ -1,3,5-triazanaphthalene	74
3-Br-2-OEt-1,5-naphthyridine	—	—	3-NH ₂ 4-NH ₂	—	22,53
3-Br-1-Et-1,5-naphthyridin-2[1 <i>H</i>]-one	—	—	3-NH ₂ 4-NH ₂	—	53
2-NH ₂ -3-Br-1,5-naphthyridine	—	—	2,3-DiNH ₂ ^b	—	52
3-X-1,6-naphthyridine (X = Cl, Br)	—	—	3-NH ₂ 4-NH ₂	—	48
4-X-1,6-naphthyridine (X = Cl, Br)	4-NH ₂	—	3-NH ₂ 4-NH ₂	—	48
2,4-DiBr-1,6-naphthyridine	^c	—	^c	4-Br-2-CH ₃ -1,3,6-triazanaphthalene 4-NH ₂ -2-CH ₃ -1,3,6-triazanaphthalene 4-NH ₂ -2-CH ₃ -1,3,7-triazanaphthalene	56
2-X-1,7-naphthyridine (X = Cl, Br)	2-NH ₂	4-NH ₂ 8-NH ₂	—	—	25
3-X-1,7-naphthyridine (X = Cl, Br)	—	—	3-NH ₂ 4-NH ₂	—	26
4-X-1,7-naphthyridine (X = Cl, Br)	4-NH ₂	—	3-NH ₂ 4-NH ₂	—	49

5-X-1,7-naphthyridine (X = Br)	—	2-NH ₂	—	—	28
(X = Cl, Br)		8-NH ₂			
8-X-1,7-naphthyridine (X = Cl, Br)	8-NH ₂	2-NH ₂	—	—	10,25
2-X-1,8-naphthyridine (X = Cl, Br)	2-NH ₂	7- (or 2-) NH ₂	—	—	10,29
3-X-1,8-naphthyridine (X = Cl, Br)	—	—	3-NH ₂	—	29
			4-NH ₂		
4-X-1,8-naphthyridine (X = Cl, Br)	4-NH ₂	—	3-NH ₂	—	29
			4-NH ₂		
1-X-2,6-naphthyridine (X = Cl, Br)	1-NH ₂	5- (or 1-) NH ₂	—	—	21
1-X-2,7-naphthyridine (X = Cl, Br)	1-NH ₂	—	—	—	30

^a In this reaction 2,4-diNH₂-1,5-naphthyridine is obtained; the amino group on position 4 is introduced via an S_N(EA) mechanism and the amino group at C-2 via an S_N(AE)^{ipso} reaction.

^b In addition to the 2,3-diNH₂ compound, a small amount of 2-amino-1,5-naphthyridine was formed due to debromination.

^c 2,4-DiNH₂-1,6-naphthyridine is formed involving both an S_N(AE)^{ipso} and an S_N(EA) mechanism.^a

^d In addition to 2-NH₂- and 8-NH₂-1,7-naphthyridine some 8-NH₂-5-X-1,7-naphthyridine was found.

V. Summary

This chapter has provided a summary of the reactions that naphthyridines can undergo with KNH_2/NH_3 . The complex behavior of these naphthyridines toward this reagent (ipso, tele, and cine substitutions, as well as ring transformations) is shown in the Table VIII.

Recent Developments in Naphthyridine Chemistry

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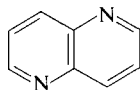
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I. Introduction

The chemistry of naphthyridines was last reviewed in this series in 1970.¹ Since that time a veritable explosion of publications has occurred emphasizing the chemistry of the naphthyridine metal complexes, their medicinal

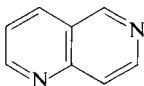
¹ W. W. Paudler and T. J. Kress, *Adv. Heterocycl. Chem.* **11**, 123 (1970).

application, and the study of the physical properties of these compounds. It is the purpose of this review to update the earlier one. Thus, publications that have appeared since 1970 will be highlighted. The group of six diazaphthalenes (1–6) that contain a nitrogen atom in each ring are referred to as naphthyridines.



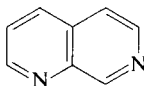
1,5-

(1)



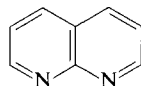
1,6-

(2)



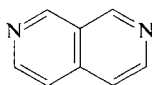
1,7-

(3)



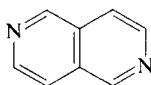
1,8-

(4)



2,7-

(5)

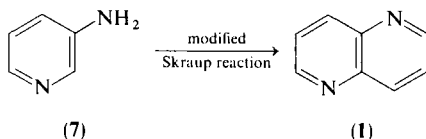


2,6-

(6)

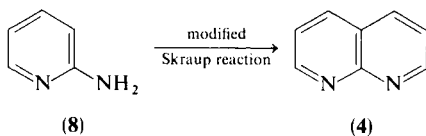
II. Syntheses of Naphthyridines²

The application of the Skraup reaction, utilizing "sulfo mix," to the appropriate aminopyridines affords these compounds in variable yields. Recent reaction condition improvements³ in some of these syntheses afford the naphthyridines in up to 90% yields.



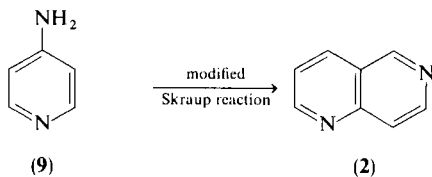
(7)

(1)



(8)

(2)



(9)

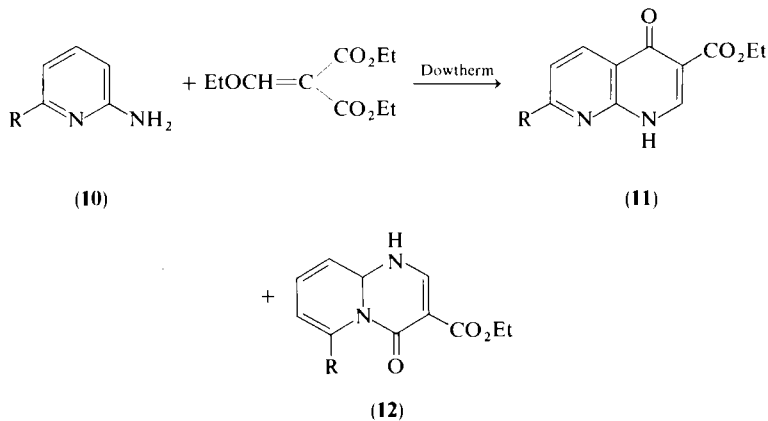
(3)

² W. Czuba, *Khim. Geterotsikl. Soedin.*, 3 (1979).

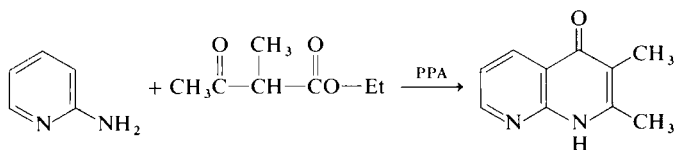
³ Y. Hamada and I. I. Takeuchi, *Chem. Pharm. Bull.* **19**, 1857 (1971).

It is again¹ pointed out that no 1,7-naphthyridine is obtained by potential cyclization into the 4-position of 3-aminopyridine, 1,5-naphthyridine (**1**) being the lone naphthyridine product. Only when the 2-position is blocked by electron-donating groups are 1,7-naphthyridines obtained.¹

The well-known reaction of 3-aminopyridines (e.g., **10**) with ethoxy-



methylene malonic esters in Dowtherm has been reexamined. High yields of the appropriate oxo compounds (e.g., **11**) along with isomeric **12** are obtained when there is a methyl, ethoxy, or alkylamino group in the 6-position. When R is an amino group (e.g., 2,6-diaminopyridine) the 7-amino-2-oxo, rather than the 7-amino-4-oxo isomer, is obtained.^{4a} An interesting variant of these cyclization reactions^{4b} involves the reaction of 2-aminopyridine with α -methylacetoacetic ester in the presence of polyphosphoric acid (PPA):



Some 1,3-dicarbonyl compounds, when condensed with 2,6-diaminopyridine, afford 2-amino-5,7-disubstituted 1,8-naphthyridines.^{4a}

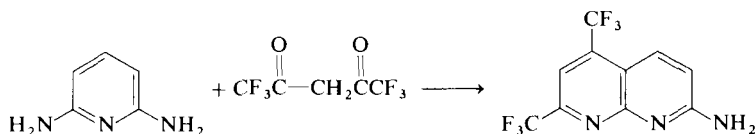
⁴ J. Pomorski, *Rocz. Chem.* **48**, 321 (1974);

J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, and C. R. Hauser, *J. Am. Chem. Soc.* **68**, 1317 (1946);

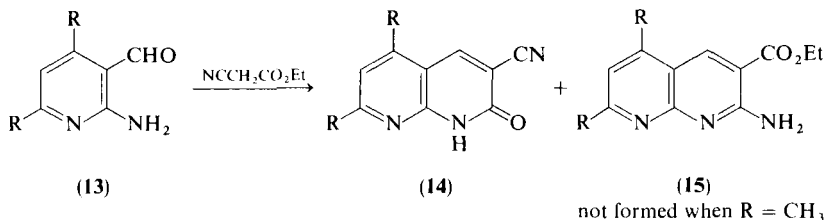
J. Heinal, H. W. Kehn, E. Dogs, A. Seeger, and C. Herrmann, *Eur. J. Med. Chem.—Chim. Ther.* 549 (1977).

^{4a} E. Eichler, C. S. Rooney, and H. W. R. Williams, *J. Heterocycl. Chem.* **13**, 41 (1976).

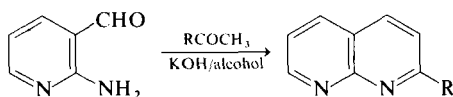
^{4b} E. B. Mullock, R. Searby, and H. Suschitzky, *J. Chem. Soc. C* **6**, 829 (1970).



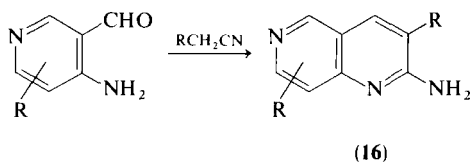
2-Aminonicotinaldehydes (**13**; $\text{R} = \text{CH}_3$) afford 1,8-naphthyridines⁵ when



condensed with the appropriate methylene compounds. In the case of 2-amino-4,6-dimethylnicotinaldehyde (**13**), cyanoacetic acid affords the 2-oxo-1,8-naphthyridine (**14**) rather than compound **15**. The prior conversion of the amino compound to the anil does not alter the course of the reaction.⁶ An extension of this cyclization involves the condensation of 2-aminonicotinaldehyde with methyl ketones in the presence of alcoholic potassium hydroxide to generate the corresponding 2-substituted 1,8-naphthyridine.⁷



When 4-amino-3-carboxaldehyde derivatives of pyridine are employed, 2-amino-1,6-naphthyridines (**16**) are obtained.⁶



Other activated methylene compounds have been used in the aldehyde cyclizations as well.⁸⁻¹¹ Aminopyridines containing an alkoxycarbonyl

⁵ J. E. Harper and D. G. Wibberley, *J. Chem. Soc. C* **18**, 2991 (1971).

⁶ E. Eichler, C. S. Rooney, and H. W. R. Williams, *J. Heterocycl. Chem.* **13**, 43 (1976).

⁷ B. Sreenivasulu and K. Reddy Vijayender, *Curr. Sci.* **46**, 597 (1977).

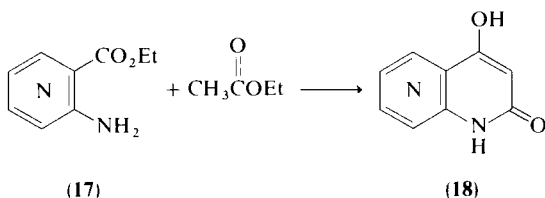
⁸ A. Decormeille, G. Quequiner, and P. Pastour, *C. R. Acad. Sci., Ser. C* 381 (1975).

⁹ E. Gudriniece and B. Rigerte, *Latv. PSR Zinat. Akad. Vesti, Kim. Ser.*, 239, (1974) [*CA* **81**, 3749Oh (1974)].

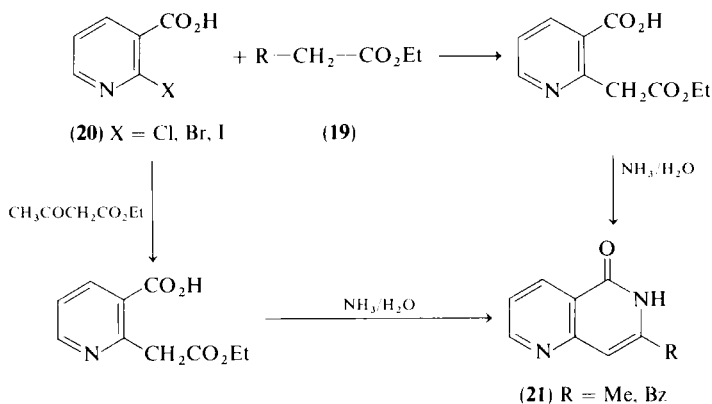
¹⁰ E. M. Hawes, D. K. J. Gorecki, and R. G. Gedir, *J. Med. Chem.* **20**, 838 (1977).

¹¹ D. K. J. Gorecki and E. M. Hawes, *J. Med. Chem.* **20**, 124 (1977).

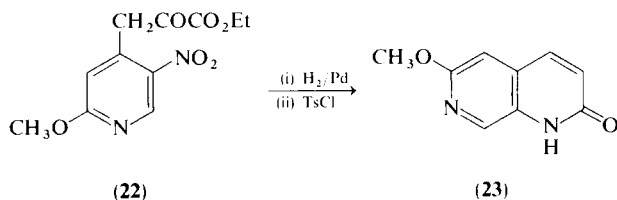
group on the carbon adjacent to the amino function (17) react with ethyl acetate to generate the corresponding 2,4-dioxonaphthyridines (18).^{12,13}



Cyclizing agents containing an active methylene group (19) react readily with 2-halonicotinic acids (20) to afford 5,7-disubstituted 1,6-naphthyridines (21) after treatment with aqueous ammonia.¹⁴



The reductive cyclization of appropriately substituted nitropyridines (e.g., 22) affords 1,7-naphthyridines (23).¹⁵ 2-Cyano-3-pyridyl acetonitrile



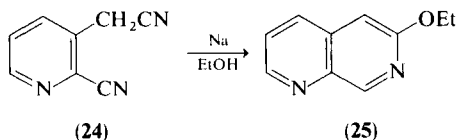
(24) yields the 1,7-naphthyridine (25) when reduced with sodium in ethanol.¹⁵

¹² W. Czuba and M. Woźniak, *Rocz. Chem.* **48**, 1815 (1974).

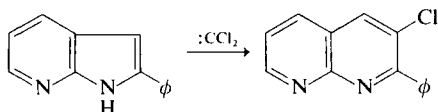
¹³ W. Czuba and M. Woźniak, *Zesz. Nauk. Univ. Jagiellon., Pr. Chem.* **20**, 61 (1975) [*CA* **82**, 57584 (1975)].

¹⁴ D. E. Ames and W. D. Dodds, *J. C. S. Perkin I* **5**, 705 (1972).

¹⁵ B. Frydman, M. Los, and H. Rapoport, *J. Org. Chem.* **36**, 450 (1971).



A rather unique synthetic example based on the well-known pyrrole–pyridine carbene insertion reaction involves the following ring expansion.¹⁶



III. Electrophilic Substitution Reactions

As already described¹ the electrophilic substitution reactions in the naphthyridines follow the “pyridine” pattern. Thus, 3-bromo derivatives are formed in all of the 1,X-naphthyridines. In addition, dibromo derivatives are formed with the second bromine at the position β to the other ring nitrogen atom. This pattern prevails when either pyridine or nitrobenzene¹⁷ is used as a solvent rather than carbon tetrachloride. Bromination of 1,5-naphthyridine *N*-oxide affords the 3,6-dibromo-1,5-naphthyridine as a minor product, apparently through prior de-*N*-oxygenation.¹⁸

A. BROMINATIONS OF HYDROHALIDE SALTS OF 1,7- AND 1,8-NAPHTHYRIDINES

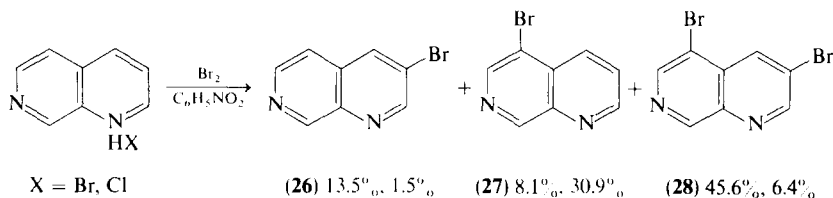
A means of brominating heterocyclic compounds (treatment of the hydrohalide of an azine with bromine in nitrobenzene) has been developed by Kress¹⁹ that gives, in some instances, superior yields to the Eisch bromination. This bromination procedure has now been applied to 1,7- and 1,8-naphthyridine.¹⁷ In the case of 1,7-naphthyridine hydrobromide, 3-bromo-, 5-bromo-, and 3,5-dibromo-1,7-naphthyridine (**26**, **27**, and **28**, respectively) are isolated. When an excess (2.5 equiv to 1) of bromine is used,

¹⁶ R. Herbert and D. G. Wibberley, *J. Chem. Soc. C* **11**, 1505 (1969).

¹⁷ H. C. van der Plas and M. Woźniak, *J. Heterocycl. Chem.* **13**, 961 (1976).

¹⁸ R. A. van Dahm and W. W. Paudler, *J. Org. Chem.* **40**, 3068 (1975).

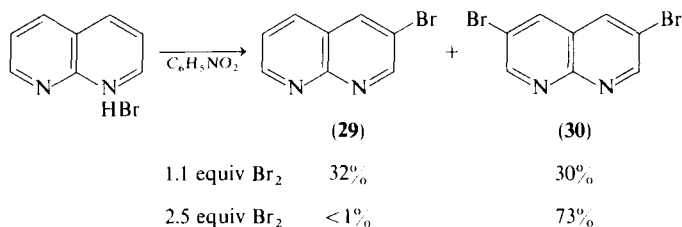
¹⁹ T. J. Kress, U.S. Patent 308,389 [*CA* **82**, 73022 (1975)].



the dibromo derivative is obtained in 75% yield. Interestingly, a significant difference in product ratio is observed when the hydrobromide salt is brominated with 1.1 equiv of bromine as compared to the hydrochloride salt reacting under identical conditions. When the hydrochloride salt is used, the products are contaminated with some chloronaphthyridines.

A further significant difference between the Eisch and Kress bromination products of 1,7-naphthyridine is that the former procedure does not yield any 3-bromo derivative. Although the Eisch procedure is preferred for the formation of the 5-bromo compound (25% yield and only traces of the 3,5-dibromo compound being formed), the Kress procedure is better for the synthesis of the 3,5-dibromo derivative (45.6% yield).

Bromination of 1,8-naphthyridine by the Kress procedure affords a 1:1 ratio of the 3-bromo (29) and 3,6-dibromo (30) derivatives when 1.1



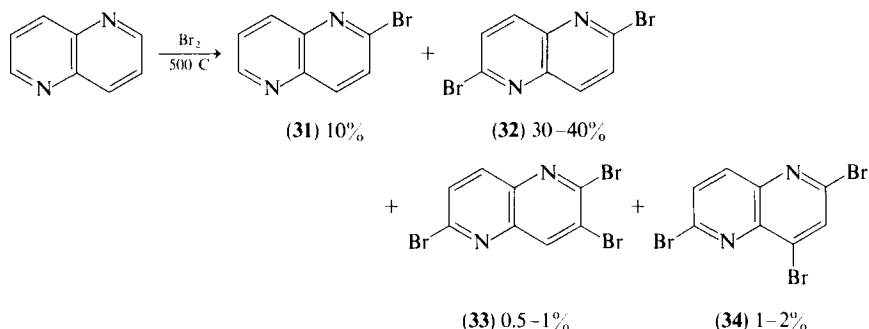
equiv of bromine are employed. In contrast, the dibromo compound is obtained in 73% yield when the bromine equivalent is 2.5. The Eisch procedure affords the monobromo compound in a 10:1 ratio over the dibromo derivative. However, the yields are exceedingly low (5%). Thus, the Kress procedure is vastly superior for the dibromination of 1,8-naphthyridine.^{14,19,20}

Although little is known about the mechanistic details governing the Eisch or Kress procedures, one possible difference between the two is that, in the former, the starting material may be a quaternary *N*-bromo derivative, whereas in the latter, it may be a quaternary NH derivative. Presumably, detailed studies of these two mechanisms will offer explanations to account for the difference between these two "electrophilic" bromination reactions.

²⁰ T. J. Kress and S. M. Constantino, *J. Heterocycl. Chem.* **10**, 409 (1973); T. J. Kress and L. L. Moore, *ibid.*, 153.

B. GAS-PHASE BROMINATION OF 1,5-NAPHTHYRIDINE

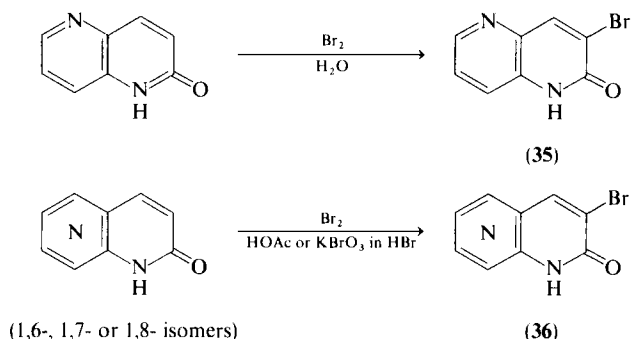
When 1,5-naphthyridine mixed with bromine is passed through a glass tube filled with pumice at 500°C, a mixture of 2-bromo-, 2,6-dibromo-, 2,3,6-tribromo-, and 2,4,6-tribromo-1,5-naphthyridines (**31**, **32**, **33**, and **34**,



respectively) are isolated in the indicated yields. As anticipated bromination under these free radical conditions affords none of the electrophilic bromination products.²¹

C. BROMINATION OF OXONAPHTHYRIDINES

As expected, the bromination of either 2-oxo- or 4-oxonaphthyridines proceeds under much milder conditions than the corresponding parent heterocyclic systems. Thus, the 3-bromo derivatives (**35** and **36**) are readily



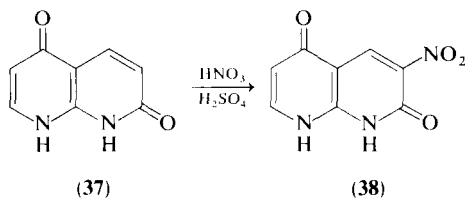
obtained under the conditions indicated in the equations.^{1,13,22,23} The

²¹ J. Pomorski and H. J. Hertog, *Rocz. Chem.* **47**, 2123 (1973).

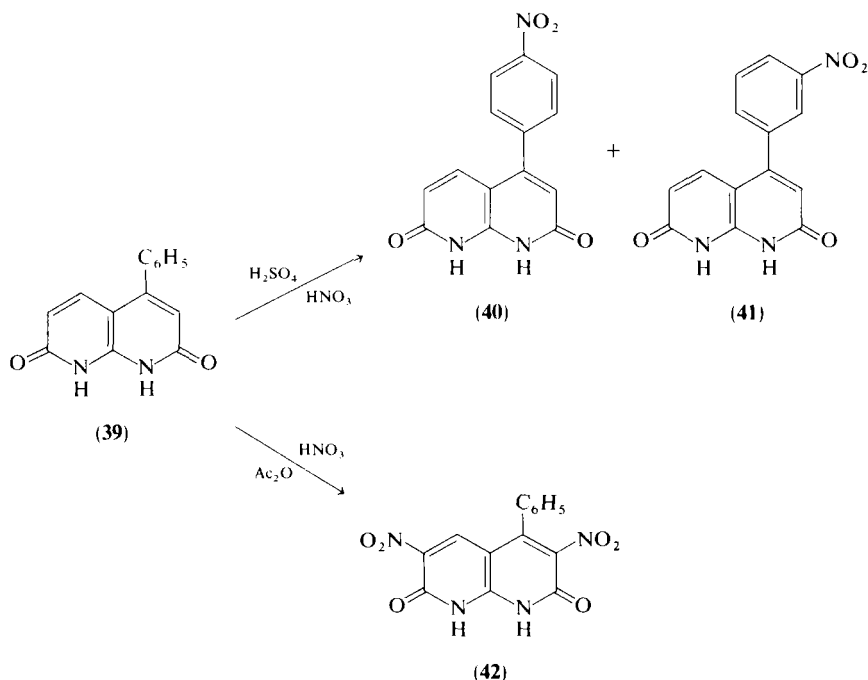
²² W. Czuba and M. Woźniak, *Recl. Trav. Chim. Pays-Bas* **93**, 144 (1974).

²³ W. Czuba and M. Woźniak, *Rocz. Chem.* **47**, 2361 (1973).

corresponding 3-chloro derivatives are obtained when KClO_3 in HCl is used as the chlorinating agent.²⁴ The 2-oxo- and 4-oxonaphthyridines are nitrated, affording the corresponding 3-nitro derivatives.^{1,25} Nitration of 2,5-dioxo derivative **37** affords the 3-nitro derivative **38**.²⁵



When a competition with potential nitration of a phenyl ring exists, as in compound **39**, the site of nitration is dependent upon the reaction conditions.²⁵ In the presence of sulfuric acid, initial nitration takes place on the



²⁴ E. V. Brown and S. Mitchell, *J. Org. Chem.* **40**, 660 (1975).

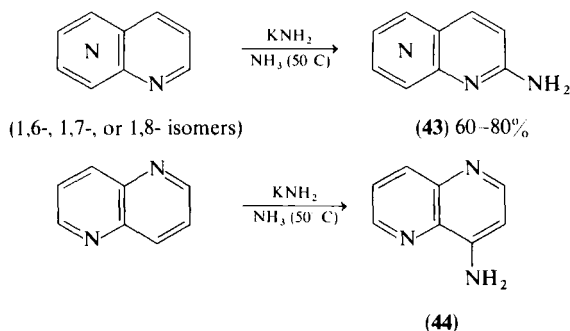
²⁵ S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, C. Mori, and I. Tonetti, *Gazz. Chim. Ital.* **102**, 253 (1972).

phenyl ring, whereas in acetic anhydride, nitration occurs exclusively in the naphthyridine rings (**42**).²⁶ Nitrophenyl compounds **40** and **41** can be further nitrated to afford the 3,7-dinitro derivatives.²⁷

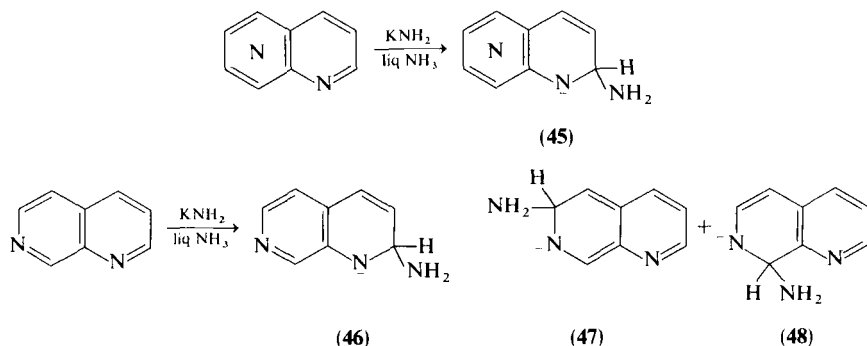
IV. Nucleophilic Substitution Reactions

For a detailed account of naphthyridine reactions with nitrogen nucleophiles, see chapter by van der Plas *et al.*, p. 95 of this volume.

The amination of the 1,6-, 1,7-, and 1,8-naphthyridines (**2**, **3**, and **4**, respectively) affords the 2-amino derivatives (**43**), whereas the 1,5-isomer yields



the 4-amino-1,5-naphthyridine (**44**).²⁷ Vastly improved yields of these compounds are obtained when these aminations are done at 50°C rather than at liquid ammonia temperatures.^{1,28} The intermediate adducts in these

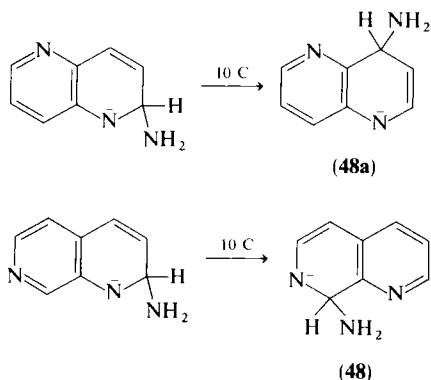


²⁶ S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I. Tonetti, *Gazz. Chim. Ital.* **104**, 499 (1974).

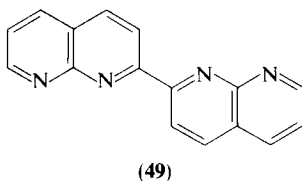
²⁷ E. V. Brown and A. C. Plas, *J. Heterocycl. Chem.* **7**, 589 (1970).

²⁸ Y. Hamada and I. Takeuchi, *Yuki Gosei Kagaku Kyokaishi* **32**, 602 (1974); *Zh. Khim.*, 6Zh382 (1975).

aminations have been identified by NMR spectroscopic analysis. In the 1,X-naphthyridine instances, the 1,2-dihydro structures (**45**) are the primary adducts. In 1,7-naphthyridine the C-6 (**47**) and C-8 (**48**) adducts are obtained^{29,30} in addition to the formation of the 1,2-dihydro adduct (**46**). It is of interest that the site of adduct formation in the 1,5- and 1,7-naphthyridines changes to C-4 (**48a**) and C-8 (**48**), respectively, when the temperature is increased from -40°C to about $+10^{\circ}\text{C}$.³¹



The 1,X-naphthyridines react with phenyllithium to afford the corresponding 2-phenyl derivatives.³² When 1,8-naphthyridine is treated with butyllithium, the 2-butyl derivative is obtained, whereas reaction of dithiane with butyl lithium followed by addition of 1,8-naphthyridine generates bisnaphthyridine **49**. An interesting application of the dimethyl sulfoxide-sodium



hydride methylation to the 1,X-naphthyridines affords dimethyl-1,X-naphthyridines **50**, **51**, and **52**, respectively.^{32,33} 1,6-Naphthyridine, when

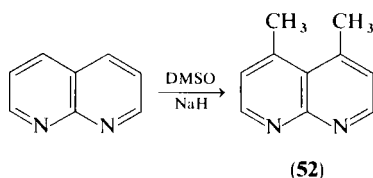
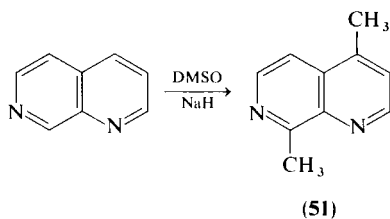
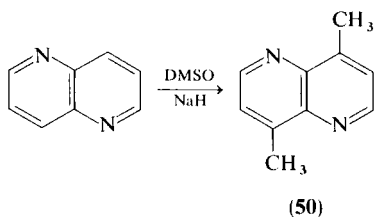
²⁹ H. C. van der Plas, A. van Veldhuisen, M. Wozniak, and P. Smit, *J. Org. Chem.* **43**, 1673 (1978).

³⁰ W. Maran, *Zesz. Nauk. Politech. Krakow.*, Chem., 111 (1979) [*CA* **93**, 71598 (1980)].

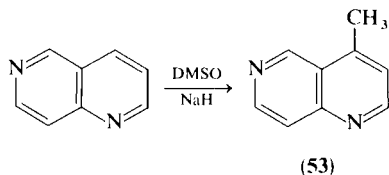
³¹ J. W. H. van Haak, H. C. van der Plas, and B. van Veldhuisen, *J. Org. Chem.* **46**, 2134 (1981).

³² Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.* **22**, 495 (1974).

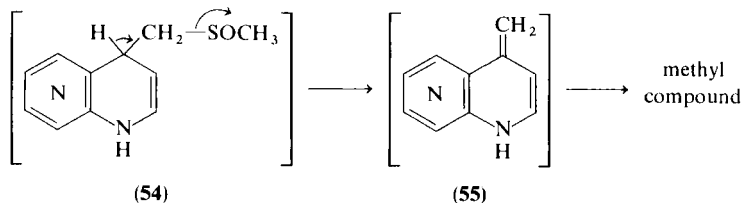
³³ Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.* **19**, 1751 (1971).



treated with DMSO/NaH, is the sole 1,X-naphthyridine that forms a mono-methyl derivative (53). Mechanistically, these compounds are formed via



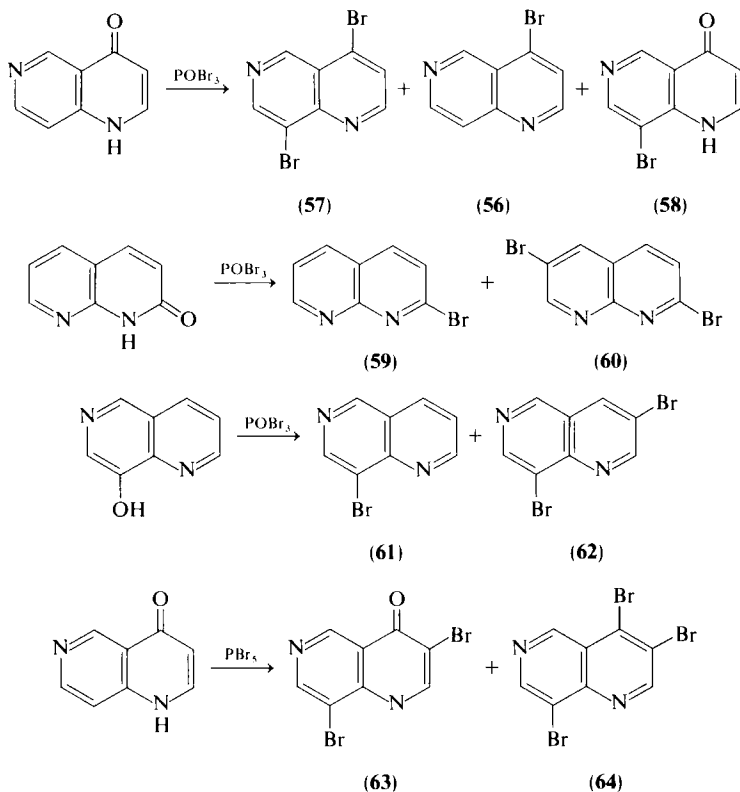
the addition compound (54) followed by elimination of CH_3SO^- to form methylene tautomer 55, which then rearranges to the observed products.



The "hydroxy" groups in 2-oxo- and 4-oxo-1,X-naphthyridines and in the corresponding 2,7-naphthyridine derivatives are readily replaced by either

chlorine³⁴ or bromine^{12,22} upon treatment with POCl_3 or POBr_3 , respectively.^{13,22,23,35,36} (PBr_5 has also been used.)

More detailed studies have established that dibromo derivatives (**57**, **60**, **62**, and **63**) are also formed in these reactions.³⁷⁻³⁹ The second bromine is always introduced at the electrophilic substitution site of the nonoxygenated



ring. The halogen in the 2-position of 2,4-dihalo-1,X-naphthyridines undergoes nucleophilic substitution more readily than the halogen at position 4. These type of reactions are exemplified by the following sequences (**65**–**77**),

³⁴ W. K. Easley and M. F. Meyer, *Proc. Acad. Sci.* **32**, 109 (1968).

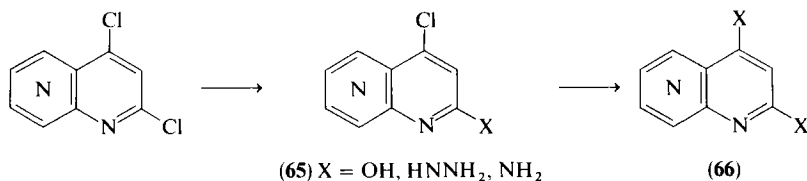
³⁵ E. Eichler, C. S. Rooney, and H. W. R. Williams, *J. Heterocycl. Chem.* **13**, 43 (1976).

³⁶ E. V. Brown and S. Mitchell, *J. Org. Chem.* **40**, 660 (1975).

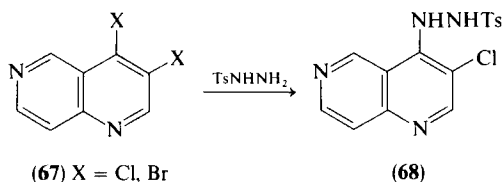
³⁷ W. W. Paudler and T. J. Kress, in "Topics in Heterocyclic Chemistry" (R. Castle, ed.), p. 109. Wiley (Interscience), New York, 1973.

³⁸ W. Czuba and T. Kowalska, in press.

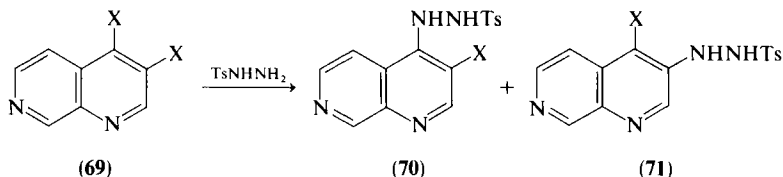
³⁹ W. W. Paudler and T. J. Kress, *J. Heterocycl. Chem.* **2**, 292 (1965).



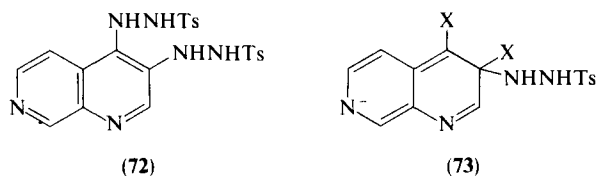
which introduce hydroxy, hydrazino, and amino groups. As might be expected, tosylhydrazine reacts selectively with the halogen in the 4-position (68) of 3,4-dihalo-1,6-naphthyridines (67).^{22,145}



In the 3,4-dihalo-1,7-naphthyridines (69)²² the replacement of the halogens is not selective, in that both halogens are ultimately displaced to form di-tosylhydrazine derivative 72. The unusual reactivity of the halogen in the



3-position is associated with the fact that intermediate 73 is stabilized by



N-7. A series of 4-chloronaphthyridines have been converted to mercapto and amino derivatives.^{34,40}

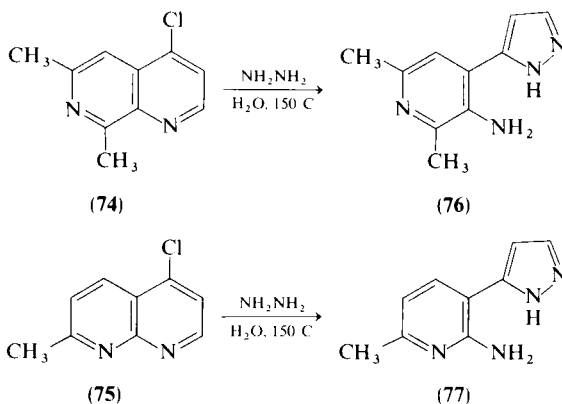
Hydrazine reacts with 4-chloro-1,7- and 4-chloro-1,8-naphthyridines (74 and 75) by cleaving the halogenated ring to generate pyrazolylpyridine derivatives (76 and 77, respectively).⁴¹⁻⁴³

⁴⁰ P. Chien and C. C. Cheng, *J. Med. Chem.* **11**, 164 (1968).

⁴¹ R. A. Bowie, *J. Chem. Soc. D* **9**, 565 (1970).

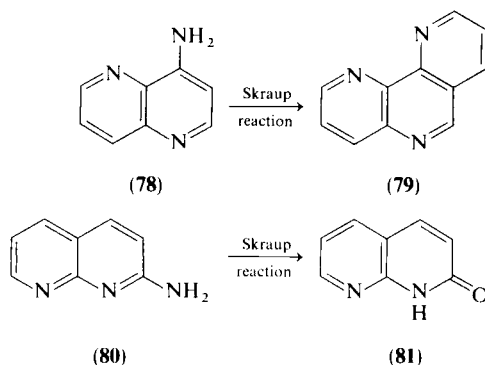
⁴² R. A. Bowie, M. J. C. Mullan, and J. F. Unsworth, *J. C. S. Perkin I* **8**, 1106 (1972).

⁴³ R. A. Bowie and B. Wright, *J. C. S. Perkin I* **12**, 1109 (1975).



A. TRANSFORMATIONS OF AMINONAPHTHYRIDINES

A logical extension of the syntheses of the 1,X-naphthyridines is the application of the Skraup reaction to aminonaphthyridines. When 4-amino-1,5-naphthyridine (78) is reacted with glycerol under Skraup reaction conditions, the expected pyrido-1,5-naphthyridine (79) is obtained.⁴⁴ When

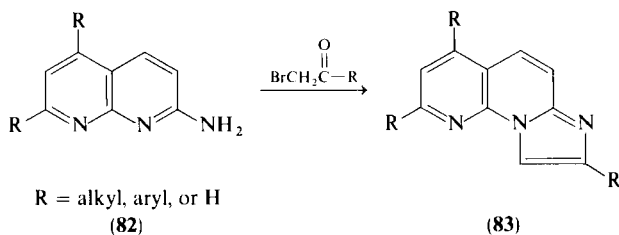


attempted on 2-amino-1,8-naphthyridine (80), the same reaction affords 2-oxo derivative **81**.⁴⁴ This facile hydrolysis of 2-amino-1,8-naphthyridine has previously been discussed.

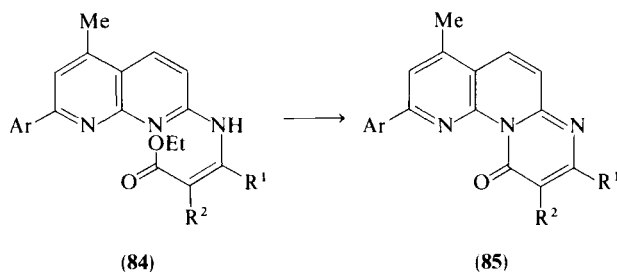
Under nonhydrolytic conditions, 2-amino-1,8-naphthyridines (**82**) do, however, undergo the "normal" cyclization reactions with α -bromo ketones. Thus, imidazo[1,2-*a*]naphthyridines (**83**) are readily obtained.⁴⁵

⁴⁴ Y. Hamada, M. Sato, and I. Takeuchi, *Yakugaku Zasshi* **95**, 1492 (1975).

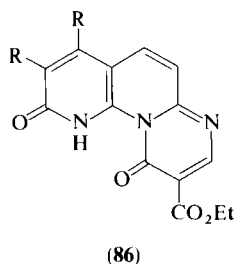
⁴⁵ J. F. Harper and D. G. Wibberley, *J. Chem. Soc. C*, 2985 (1971).



Ethyl acetoacetate, ethyl ethoxymethylenemalonate, ethyl acetoacetate, and ethyl cyanoacetate afford 2-(ethoxycarbonylvinylamino)-1,8-naphthyridines (84). Some of these compounds have been successfully cyclized to pyrimido[1,2-*a*]-1,8-naphthyridines (85).⁴⁵



Similar conversions have been accomplished on 2-amino-7-oxo-1,8-naphthyridines, whereby angular structure 86 is obtained.⁴⁵ 2-Amino-

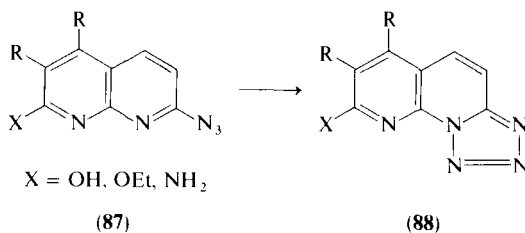


1,8-naphthyridines, following conversion to the corresponding chloro compounds, have been transformed to the 2-azido-1,8-naphthyridines (87), a type of compound that instantly cyclizes into tetrazolo form 88.⁴⁶⁻⁴⁸

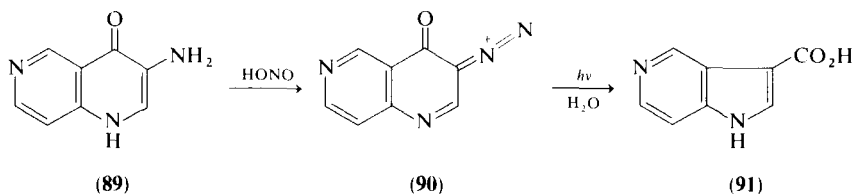
⁴⁶ S. Carboni, A. Da Settmio, and P. L. Ferrarini, *Gazz. Chim. Ital.* **97**, 42 (1967).

⁴⁷ S. Carboni, A. Da Settimo, and P. L. Ferrarini, *J. Heterocycl. Chem.* **7**, 1037 (1970).

⁴⁸ P. L. Ferrarini, *Ann. Chim. (Rome)* **61**, 318 (1971).



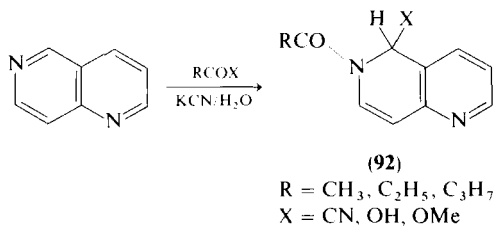
The well-known photochemical transformation of α -diazo ketones to ring-contracted derivatives also occurs when 3-amino-4-oxo-1,6-naphthyridine **89** is treated with nitrous acid and the α -diazo ketone **90** is photo-



chemically converted to azaindole **91**.⁴⁹ Similar ring-contraction reactions have been observed in the other isomeric 3-amino-4-oxo-1,X-naphthyridines.⁵⁰

B. THE REISSERT REACTION

When 1,6-naphthyridine is reacted with potassium cyanide and with an acyl or aroyl halide, the 5,6-addition product (**92**) is obtained in poor yields



unless diphenylcarbamoyl chloride is used as the acylating agent.^{51,52} The benzo-1,7-naphthyridine (**93**) gives the expected addition products (**94**) resulting from addition to the 7,8-bond of the 1,7-naphthyridine ring.⁵³

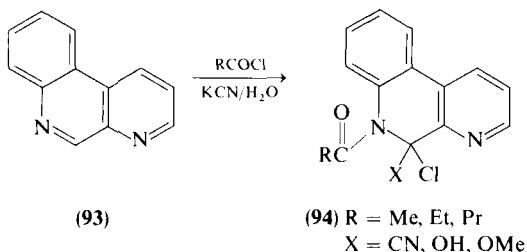
⁴⁹ T. Alder and A. Albert, *J. Chem. Soc.*, No. 4, 1794 (1960).

⁵⁰ O. Suss and K. Moller, *Justus Liebigs Ann. Chem.* **223**, 599 (1956).

⁵¹ Y. Hamada, I. Takeuchi, and M. Matsuoka, *Chem. Pharm. Bull.* **18**, 1026 (1970).

⁵² Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* **17**, 2614 (1969).

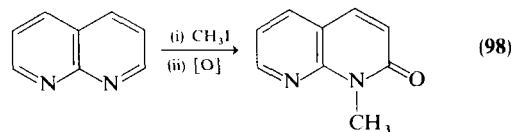
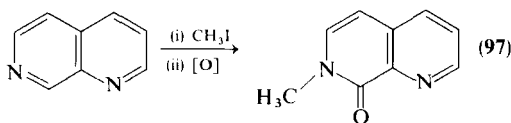
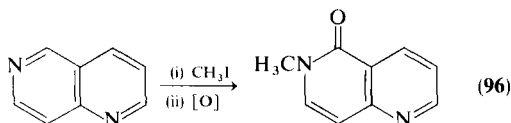
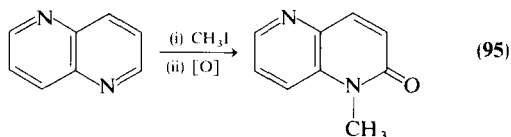
⁵³ Y. Hamada, K. Morishita, and M. Hirota, *Chem. Pharm. Bull.* **26**, 350 (1978).



V. Reactions on Nitrogen

A. *N*-ALKYL DERIVATIVES

The naphthyridines undergo *N*-alkylation reactions as expected. Thus, N-6 and N-7 are methylated first in 1,6- and in 1,7-naphthyridine, respectively. The quaternary *N*-methyl salts are oxidized by potassium ferricyanide to afford the *N*-methyl- α -one derivatives (**95–98**).^{54–56} The kinetics of



⁵⁴ Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.* **19**, 1751 (1971).

⁵⁵ J. W. Bunting, *J. C. S. Perkin I* **15**, 1833 (1974).

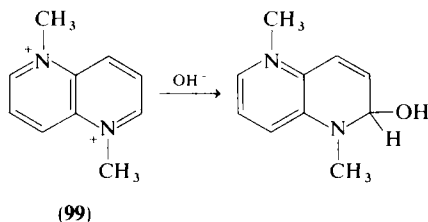
⁵⁶ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **50**, 917 (1972).

TABLE I
SECOND-ORDER RATE CONSTANTS
FOR METHIODIDE FORMATION IN
ACETONITRILE AT 24.8 ± 0.1 C

Compound	$10^{-4} k, \text{m}^{-1} \text{s}^{-1}$
Quinoline	0.517
Isoquinoline	4.23
1,5-Naphthyridine	0.232
1,6-Naphthyridine	1.66
1,8-Naphthyridine	4.25

quaternization and the structure of the pseudo bases are a recent addition to the knowledge of these quaternary compounds. Table I lists the second-order rate constants for methiodide formation of a number of naphthyridines.⁵⁷ These data clearly show that the additional nitrogen in 1,5-naphthyridine relative to quinoline decreases the charge density on the nitrogen atom being alkylated. The 1,6-naphthyridine alkylation rate constant is the sum of the separate constants for reaction at the two nitrogen atoms. The 20-times greater rate of alkylation of 1,8-naphthyridine versus that of 1,5-naphthyridine may reflect the interaction of the methyl group with the *peri*-lone pair of electrons in the 1,8-isomer.^{55,56}

The di-*N*-alkyl derivatives of 1,5- and 1,8-naphthyridine have significantly different properties. Diquaternary salt **99** is relatively stable in neutral solution, whereas **100** exists in equilibrium with its pseudo base (**101**).^{58,59} A similar pseudo base structure (**103**) has been identified⁶⁰ in the 1,8-bridged compound (**102**). The 1,5-naphthyridine salt (**99**) is readily reduced by a one-electron transfer process to give a fairly stable green radical cation (**104**).

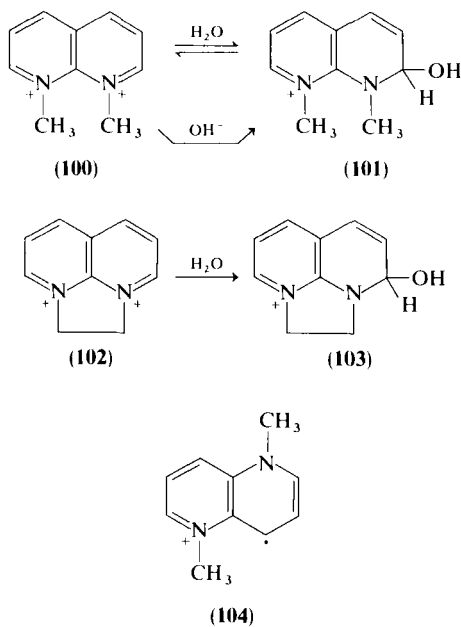


⁵⁷ R. A. Y. Jones and N. Wagstaff, *J. C. S. Chem. Commun.*, **56** (1969).

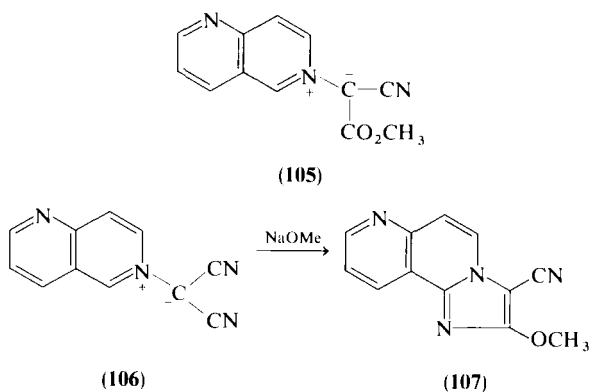
⁵⁸ D. J. Pokorny and W. W. Paudler, *Can. J. Chem.* **51**, 576 (1973).

⁵⁹ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **52**, 962 (1974).

⁶⁰ J. W. Bunting, *J. C. S. Perkin I* **15**, 1833 (1974).



In contrast, the **102** salt does not form a radical.⁶¹ Methyl bromocyanoacetate reacts with 1,6-naphthyridine to form a stable ylide **(105)**⁶² and with



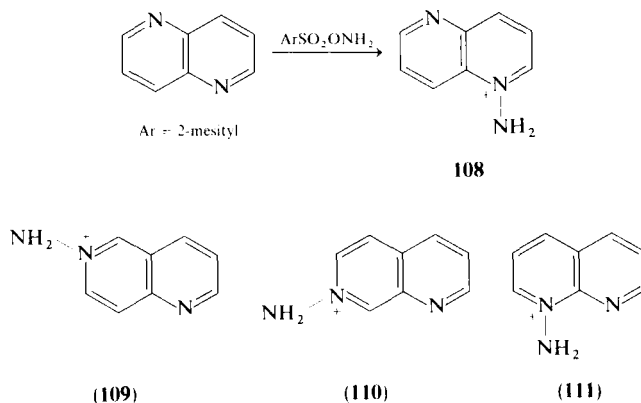
tetracyanoethylene to afford **106**. When **106** is treated with sodium methoxide it affords the imidazo[1,2-*a*]pyridine derivative **(107)**.⁶²

⁶¹ J. E. Dickeson, I. F. Eckhard, R. Fielden, and L. A. Summers, *J. C. S. Perkin I*, 2885 (1973).

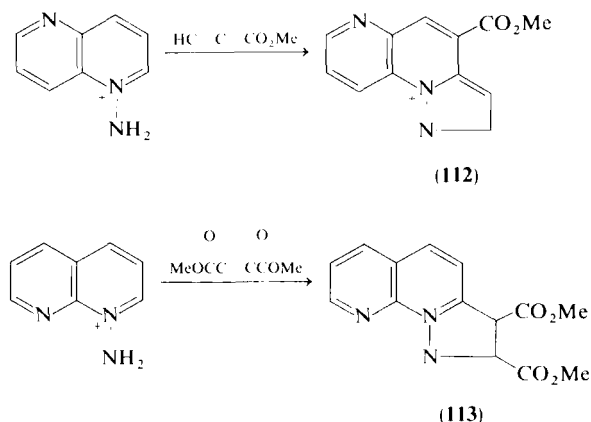
⁶² Y. Kobayashi, P. Kutsuma, K. Morinaga, F. Fujito, and Y. Hanzawa, *Chem. Pharm. Bull.* **18**, 2489 (1970).

B. *N*-AMINO DERIVATIVES

The 1,*X*-naphthyridines react with *O*-mesitylenyl sulfonylhydroxylamine to generate the *N*-amino compounds (108–111).^{63–66} These compounds are



readily benzoylated. 1,3-Dipolar cycloadditions⁶⁵ have been accomplished on the 1,5- and 1,8-naphthyridine *N*-imides to afford tricyclic derivatives (112 and 113).



⁶³ Y. Tamura, J. Minamikawa, Y. Miki, S. Malsugashita, and M. Ikeda, *Tetrahedron Lett.* **40**, 4133 (1972).

⁶⁴ Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 675 (1974).

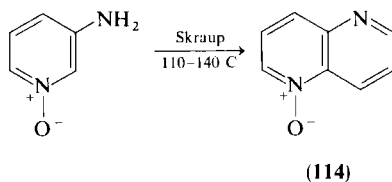
⁶⁵ Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 119 (1975).

⁶⁶ Unpublished results from authors' laboratory.

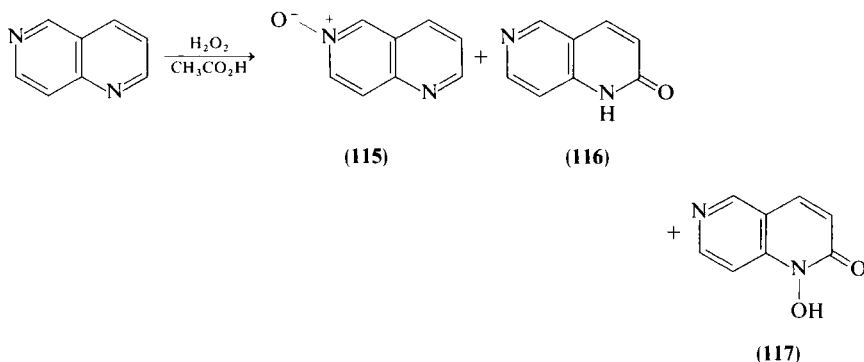
C. N-OXIDES

All of the 1,X-naphthyridines can be N-oxidized. For 1,6- and 1,7-naphthyridine the 6- and 7-oxides are formed initially. No 1,8-naphthyridine di-N-oxide has been prepared.⁶⁷⁻⁷⁰

The Skraup reaction on 3-aminopyridine N-oxide yields N-oxide **114** in good yield³⁴ or, at 150°C, 1,5-naphthyridine itself.



The N-oxidation of 1,6-naphthyridine with hydrogen peroxide in acetic acid forms the 2-oxo (**116**) and 1-hydroxy-2-oxo derivatives (**117**), along



with the 6-oxide (**115**).⁷¹ 2-Amino-1,5-naphthyridine (**118**), when treated with hydrogen peroxide and sodium tungstate, forms the 1,5-di-N-oxide (**119**) in good yield.⁷⁰

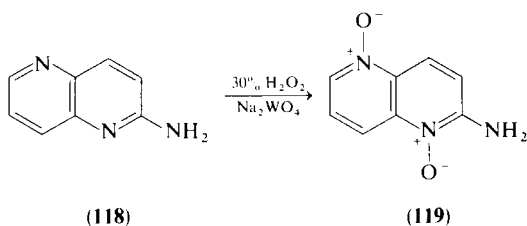
⁶⁷ E. P. Hart, *J. Chem. Soc.* **6**, 1879 (1954).

⁶⁸ U. Petrov and B. Sturgeon, *J. Chem. Soc.* **4**, 1157 (1949).

⁶⁹ W. W. Paudler, D. J. Pokorny, and S. Cornrich, *J. Heterocycl. Chem.* **7**, 291 (1970).

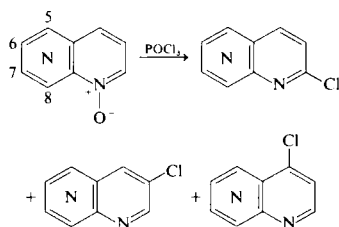
⁷⁰ R. M. Titkova, A. S. Elina, and N. P. Kostyuchenko, *Khim. Geterotsikl. Soedin.*, 1237 (1972).

⁷¹ T. Takahashi, Y. Hamada, I. Takeuchi, and H. Uchiyama, *Yakugaku Zasshi* **89**, 1260 (1969).



The Meisenheimer reaction of the 1,X-naphthyridine 1-oxides has been examined in some detail.⁷²⁻⁷⁵ Table II lists the relative yields of the 2-, 3-, and 4-chloronaphthyridines formed. As the amount of 2-chloronaphthyridine decreases, the 3-chloro and 4-chloro isomers increase in the series 1,7-, 1,5-, 1,8-, and 1,6-naphthyridine.

TABLE II
MEISENHEIMER REACTION PRODUCTS
FROM 1,X-NAPHTHYRIDINE 1-OXIDES



	Relative yields (%)		
1,5-Naphthyridine	42	3	54 ⁷²
1,6-Naphthyridine	12	20	66 ⁷²
1,7-Naphthyridine	56	3	35 ⁷³
1,8-Naphthyridine	36	7	57 ⁷³

The 2-chloro compound may be formed via an intramolecular process, whereas an intermolecular route may be operative in the formation of the 4-chloro compound.⁷³ The 3-chloro isomer, however, could be formed through a modified electrophilic substitution process.

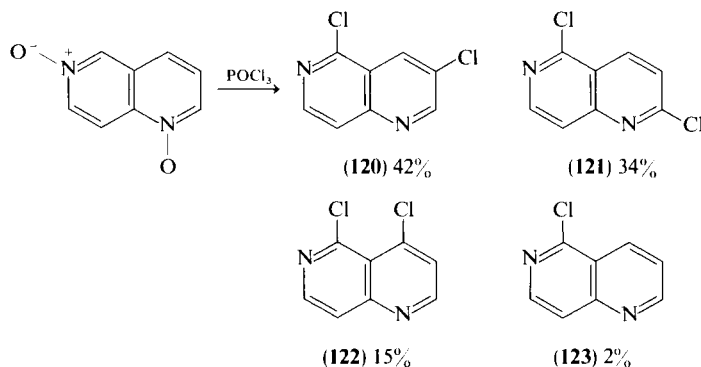
⁷² W. W. Paudler and D. J. Pokorny, *J. Org. Chem.* **36**, 1720 (1971).

⁷³ D. J. Pokorny and W. W. Paudler, *J. Org. Chem.* **37**, 3101 (1972).

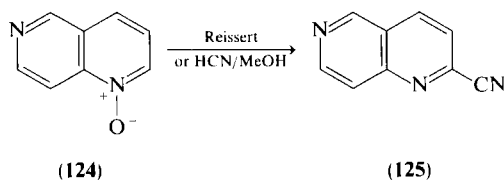
⁷⁴ E. V. Brown and A. C. Plas, *J. Org. Chem.* **36**, 1331 (1971).

⁷⁵ D. J. Pokorny and W. W. Paudler, *J. Heterocycl. Chem.* **9**, 1151 (1972).

Phosphorus oxychloride converts 1,6-naphthyridine 1,6-dioxide to a mixture of 2,5-dichloro-, 3,5-dichloro-, 4,5-dichloro-, and 5-chloro-1,X-naphthyridines (**121**, **120**, **122**, and **123**, respectively). The 3,5- and 2,5-dichloro isomers are formed as the major products.



The Reissert reaction with 1,6-naphthyridine-1-oxide (**124**), as well as with HCN in methanol, forms 2-cyano-1,6-naphthyridine (**125**).

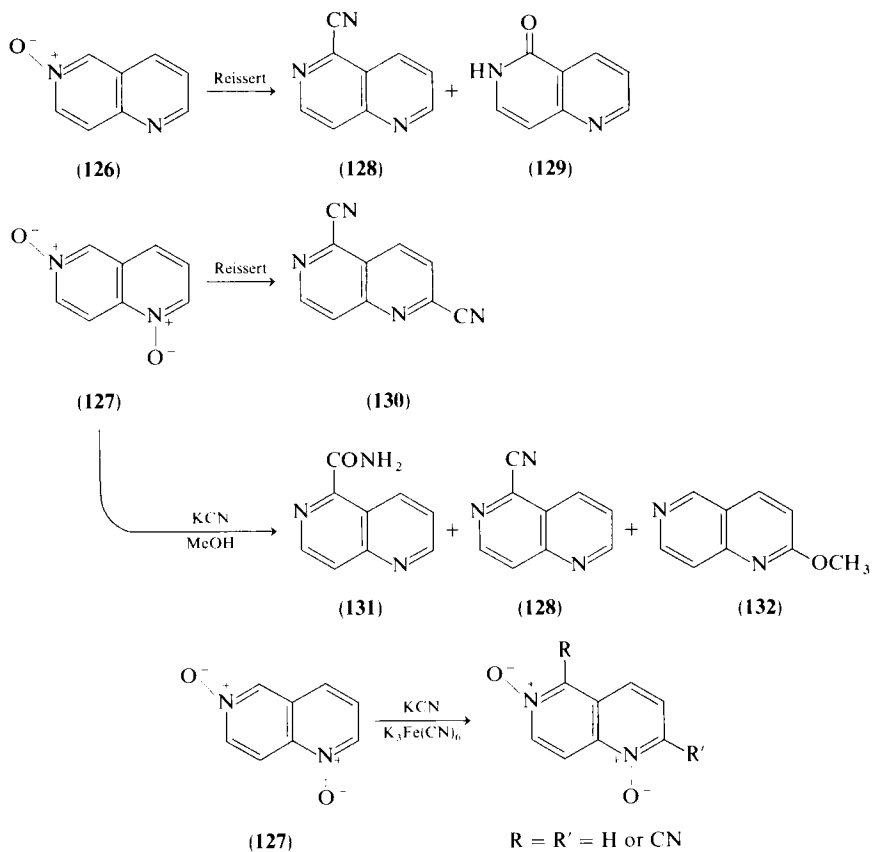


The 1,6-naphthyridine-6-oxide (**126**) and 1,6-naphthyridine-1,6-dioxide (**127**) form the 5-cyano (**128**) and 2,5-dicyano (**130**) compounds, respectively, when subjected to Reissert reaction conditions.⁵² The 5-oxo isomer (**129**) is a by-product in the 6-oxide reaction. Cyano-1,6-naphthyridines are obtained when the 1,6-di-*N*-oxide (**127**) is treated with potassium cyanide in the presence of potassium ferricyanide.^{76,77} Methanolic potassium cyanide yields the 5-cyano-, 5-carboxamido-, and 2-methoxy-1,6-naphthyridines (**128**, **131**, and **132**, respectively) when reacted with 1,6-naphthyridine 1,6-dioxide (**127**).⁷⁸

⁷⁶ Y. Kobayashi, I. Kumadaki, and H. Sato, *J. Org. Chem.* **37**, 3588 (1972).

⁷⁷ Y. Hamada, I. Takeuchi, and M. Matsuoka, *Chem. Pharm. Bull.* **18**, 1026 (1970).

⁷⁸ Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* **18**, 861 (1970).



VI. Reduced Naphthyridines

Tetrahydro- (133) and *trans*-decahydronaphthyridines (134) can be selectively prepared from the parent ring systems by reduction in the presence of either platinum oxide or palladium or by reduction with sodium in ethanol or amyl alcohol.⁷⁹⁻⁸³ Hydrogenation in acetic acid with platinum catalyst affords a *cis*- and *trans*-decahydro mixture (135 and 134).⁸¹

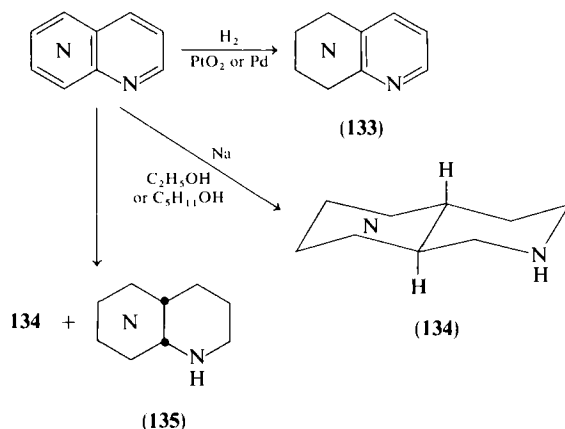
⁷⁹ K. Miyaki, *J. Pharm. Soc. Jpn.* **62**, 26 (1942).

⁸⁰ E. Ochiai and K. Miyaki, *Ber. Dtsch. Chem. Ges.* **74** 1115 (1941).

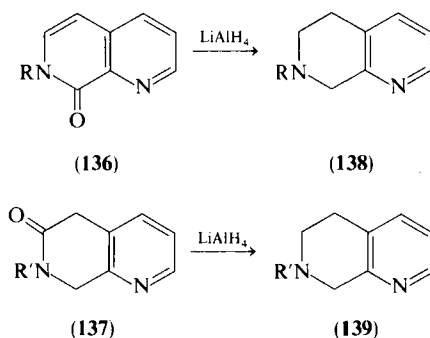
⁸¹ W. L. F. Armarego, *J. Chem. Soc. C* **5**, 377 (1967).

⁸² N. Ikekawa, *Chem. Pharm. Bull.* **6**, 408 (1958).

⁸³ J. Pomorski, *Arch. Immunol. Ther. Exp.* **19**, 261 (1971).



Lithium aluminum hydride converts oxo compounds **136** and **137** to 5,6,7,8-tetrahydronaphthyridines **138** and **139**, respectively.⁸⁴ Butyllithium



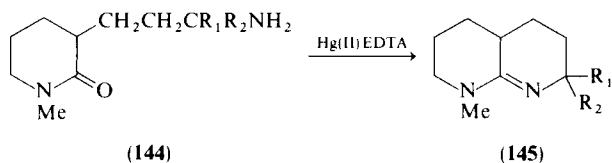
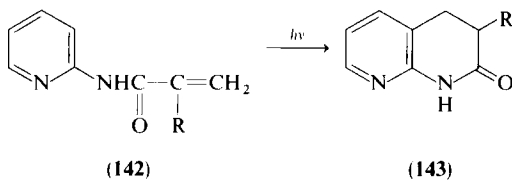
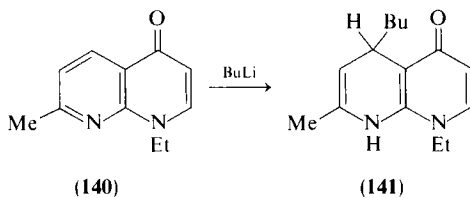
adds to the pyridine ring in oxo compound **140** to form **141**.⁸⁵ An interesting photochemical cyclization (**142** \rightarrow **143**) generates a tetrahydro-1,8-naphthyridine.⁸⁶ An oxidative cyclization involving substituted piperidones (such as **144**) affords octahydronaphthyridines of general structure (**145**).⁸⁷ 1,2,3,4-tetrahydro-2,6-naphthyridine (**148**) is obtained as shown in the transfor-

⁸⁴ S. Yoshinobu, *Chem. Pharm. Bull.* **8**, 427 (1960).

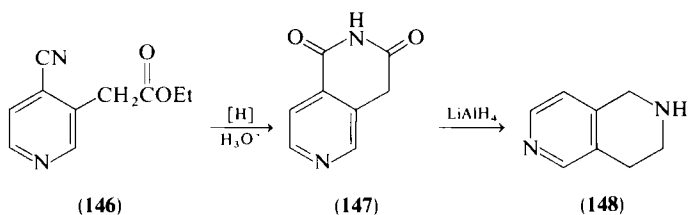
⁸⁵ J. J. Artus, J. J. Bonet, and A. E. Pena, *J. C. S. Chem. Commun.*, **579** (1973).

⁸⁶ M. Ogata and H. Matsumoto, *Chem. Pharm. Bull.* **20**, 2264 (1972).

⁸⁷ H. Moehrle and F. Specks, *Arch. Pharm. (Weinheim, Ger.)* **308**, 499 (1975).



mations **146** \rightarrow **147** \rightarrow **148**. Catalytic reduction of 2,6-naphthyridine itself affords the same tetrahydro isomer.⁸⁸

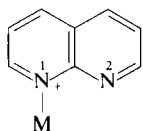


VII. 1,8-Naphthyridines as Ligands

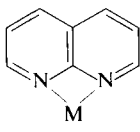
The availability of 1,8-naphthyridine and its alkyl derivatives has spawned a veritable explosion of studies aimed at examining the behavior of this ring system as a ligand. Much of this work has been done by Hendricker and co-workers, initially caused by the availability of 1,8-naphthyridine synthesized by Kress and Paudler.

⁸⁸ F. Alhaique, F. M. Ricciari, and L. Campanella, *Ann. Chim. (Rome)* **62**, 239 (1972).

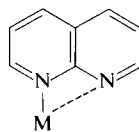
Metal ion complexes with 1,8-naphthyridine could be conceived as possessing any or all of the following structures (*a*, *b*, or *c*):



(a)



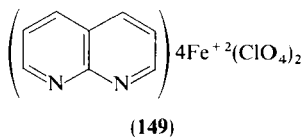
(b)



(c)

The monodentate behavior exemplified by *a* could also involve an equilibrium between the structure shown and the corresponding species where M is bonded to N₂.

Among the first complexes studied were the Fe(II) perchlorates (**149**)^{89,90} and the corresponding Mn(II), Ni(II), Cu(II), Zn(II), Pd(II), and Cd(II)⁹¹ compounds.⁹²



The X-ray crystallographic structure of the Fe(II) complex showed that the 1,8-naphthyridine was part of an eight-coordinate Fe(II) complex in which one of the 1,8-naphthyridines is more tightly bonded than the other three.⁹⁰ In solution the complex dissociates into a tris-1,8-naphthyridine-Fe(II) species.

The Mössbauer ⁵⁷Fe spectrum of the Fe(II) complex has shown that it has the largest quadrupole splitting (4.49 mm/sec) thus far encountered for any Fe(II) species.^{92,93}

These unique eight-coordinate complexes of the first-row transition metal ions maintain the four-membered chelate ring even in solution, where they dissociate into the tris-complex species.⁹⁴⁻⁹⁷

⁸⁹ D. G. Hendricker and R. L. Bodner, *Nucl. Chem. Lett.* **6**, 187 (1970).

⁹⁰ A. Clearfield, P. Sing, and I. Bernal, *J. C. S. Chem. Commun.*, 389 (1970).

⁹¹ J. M. Epstein, J. C. Dewan, D. L. Kepert, and O. H. White, *J. C. S. Dalton*, 1949 (1974).

⁹² R. L. Bodner and D. G. Hendricker, *Nucl. Chem. Lett.* **6**, 421 (1970).

⁹³ E. König, R. Ritker, E. Lindner, and I. P. Lorenz, *Chem. Phys. Lett.* **13**, 70 (1972).

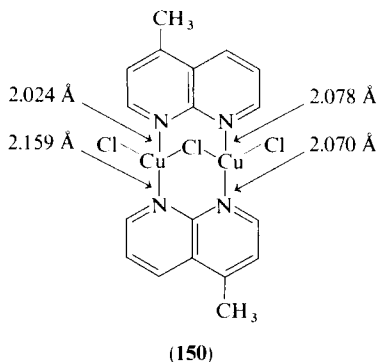
⁹⁴ M. A. Cavanough, U. M. Coppo, C. J. Alexander, and M. L. Good, *Inorg. Chem.* **15**, 2615 (1976).

⁹⁵ E. Dittmer, C. J. Alexander, and M. L. Good, *J. Coord. Chem.* **2**, 69 (1972).

⁹⁶ D. G. Blight and D. L. Wispert, *Inorg. Chem.* **11**, 1556 (1972).

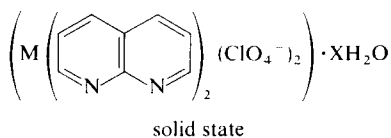
⁹⁷ I. Bertini and D. Gatteschi, *Inorg. Chem.* **12**, 2740 (1973).

A binuclear complex of 4-methyl-1,8-naphthyridine (**150**) has been prepared.⁹⁸⁻¹⁰⁰ Its structure, as determined by X-ray diffraction, shows two nearly equivalent copper atoms in a pseudotetrahedral environment bridged by one chlorine and two 4-methyl-1,8-naphthyridine rings.



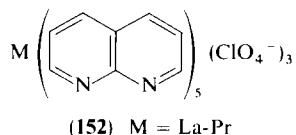
The difference of about 0.14 Å observed in the Cu—N distance (2.16–2.02 Å) at one of the copper sites has been attributed to the steric requirements of the bridged structure.¹⁰⁰

The alkaline earths, Mg, Ca, Sr, and Ba, also form four-membered chelate systems with 1,8-naphthyridine and its 2,7-dimethyl derivative (**151**).¹⁰¹ When dissolved in polar media the complexes show 3-ion conductance.



(151) M = Mg, Ca, Sr, Be

Some 10 (**152**), and possibly 12, coordinate complexes have been described,^{102,103} and some of their infrared spectra have been analyzed.¹⁰⁴



⁹⁸ D. Gatteschi, C. Mealli, and L. Saccani, *Inorg. Chem.* **15**, 2774 (1976).

⁹⁹ A. Emad and K. Emerson, *Inorg. Chem.* **11**, 2288 (1972).

¹⁰⁰ K. Emerson, A. Emad, R. W. Brookes, and R. L. Martin, *Inorg. Chem.* **12**, 978 (1973).

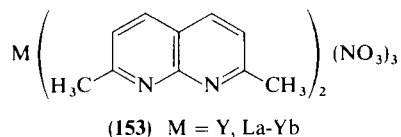
¹⁰¹ R. L. Bodner and D. G. Hendricker, *Inorg. Chem.* **9**, 1255 (1970).

¹⁰² D. G. Hendricker and R. J. Foster, *J. Inorg. Nucl. Chem.* **34**, 1949 (1972).

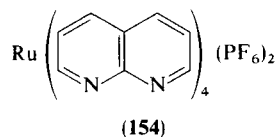
¹⁰³ R. J. Foster, R. L. Bodner, and D. G. Hendricker, *J. Inorg. Nucl. Chem.* **34**, 3795 (1972).

¹⁰⁴ B. Hutchinson and A. Sunderland, *Inorg. Chem.* **11**, 1948 (1972).

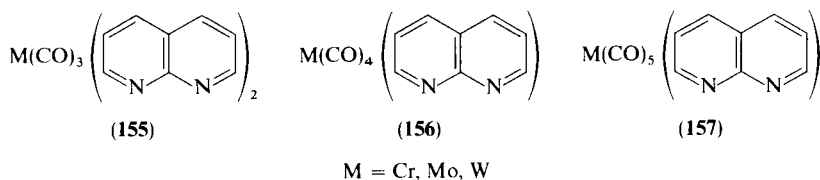
Ten-coordinate complexes using 2,7-dimethyl-1,8-naphthyridine (**153**) have been synthesized as well.¹⁰²



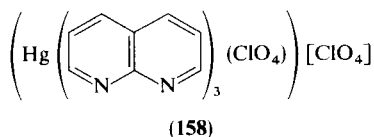
Intensely colored (near 450 nm) complexes involving Ruthenium (**154**) and 1,8-naphthyridine and its more basic derivative, 2,7-dimethyl-1,8-naphthyridine, have recently been described.¹⁰⁵ The highly colored nature of these complexes has been ascribed to metal-to-ligand charge transfer transitions.



The metal carbonyls lend themselves to complexation with 1,8-naphthyridines in a manner where they behave as both mono and bidentate ligands of general structures **155**–**157**,¹⁰⁶ depending on the number of carbonyl ligands.



One example of a seven-coordinate complex (**158**) involving three coordinated bidentatenaphthyridines and one perchlorate bonded to the metal through one of its oxygen atoms has also been prepared.⁹¹

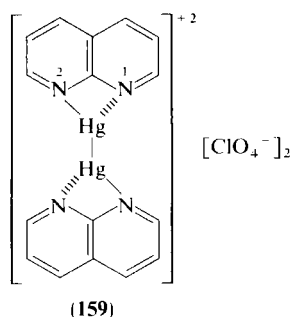


A variant of this complex is bis[(1,8-naphthyridine)mercury(I)]diperchlorate (**159**).¹⁰⁷ In this instance, the 1,8-naphthyridine behaves largely in a unidentate fashion, as shown by the fact that the N₁—Hg bond distance is

¹⁰⁵ R. J. Glaniewicz and D. J. Hendricker, *J. Am. Chem. Soc.* **99**, 6581 (1977).

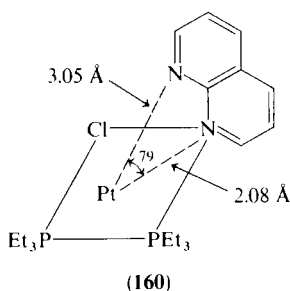
¹⁰⁶ T. E. Reed and D. G. Hendricker, *J. Coord. Chem.* **2**, 83 (1972).

¹⁰⁷ J. C. Dewan, D. L. Kepert, and A. H. White, *J. C. S. Dalton*, 4901 (1975).

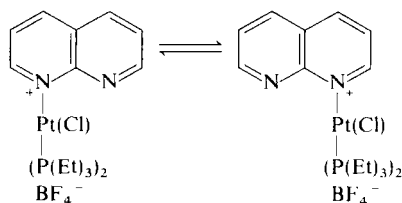


2.78 Å, whereas the N₂—Hg distance is 2.03 Å. The Hg—Hg bond in this compound is extremely short. The 1,8-naphthyridine nickel complex, [Ni₂(1,8-naphthyridine)₄Br₂]⁺ PF₆[−], also has a very short metal–metal bond length. However, all four of the naphthyridines are bridge-bonded and each metal atom is coordinated in a square-planar array by four nitrogen atoms.¹⁰⁸

The platinum 1,8-naphthyridine complex (160) in the solid state shows square-planar coordination about platinum with the naphthyridine behaving essentially as a monodentate heterocycle.¹⁰⁹



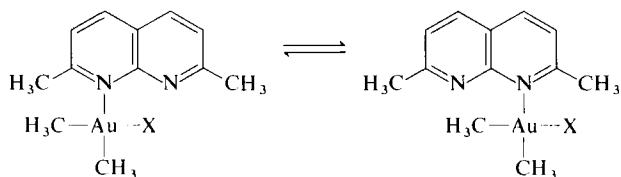
The solution proton NMR spectrum of the compound shows the naphthyridine protons to be equivalent at −30 °C or higher. Thus, under these conditions the complex shows fluxional behavior as exemplified by the following:



¹⁰⁸ D. Gatteschi, C. Mealli, and L. Saccari, *J. Am. Chem. Soc.* **95**, 2736 (1973).

¹⁰⁹ K. R. Dixon, *Inorg. Chem.* **16**, 261 (1977).

Similar fluxional behavior has been observed for dimethyl gold complexes of 2,7-dimethyl-1,8-naphthyridine.¹¹⁰ In methylene chloride or chloroform the intermolecular exchange is rapid on the NMR time scale at ambient temperatures, whereas below 200°K, the exchange is sufficiently slow to give two different sets of proton signals. Thus, the equilibrium that exists can be described by the following equation:

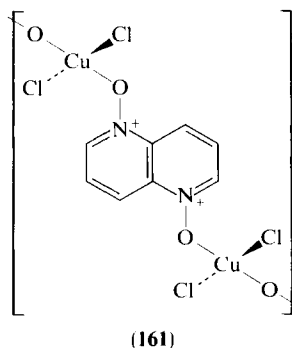


A detailed study of the infrared spectra of a number of 1,8-naphthyridine-metal complexes has established that the M—N stretching vibrations decrease consistently when the complexes containing a four-membered ring are compared with similar complexes in which the ligand is α,α' -bipyridine. Thus, this technique lends itself admirably to the structure determination of these complexes.^{104,111}

The reactions of 1,8-naphthyridine with tris(dipivaloylmethanato)lanthanide to form the appropriate complexes are exothermic.¹¹²

VIII. 1,5-Naphthyridine-1,5-dioxide Complexes

The title compound forms coordination compounds with Cu(II) chloride, bromide, and nitrate. The postulated structure of these compounds is 161.¹¹³



¹¹⁰ A. Schmidbaur and K. C. Dosh, *J. Am. Chem. Soc.* **95**, 4855 (1973).

¹¹¹ B. Hutchinson, A. Sunderland, M. Neal, and S. Olbricht, *Spectrochim. Acta* **29**, 2001 (1973).

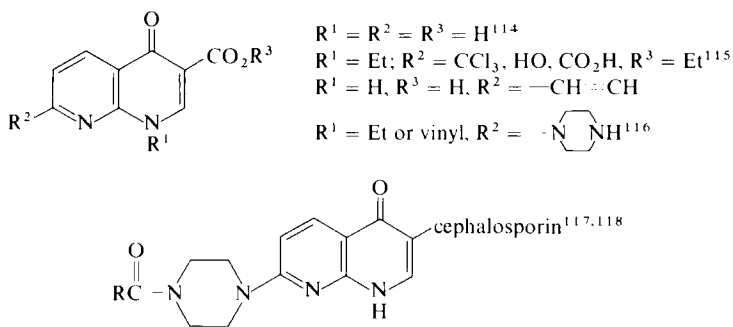
¹¹² D. R. Dakternieks, *J. Inorg. Nucl. Chem.* **38**, 141 (1976).

¹¹³ H. W. Richardson, J. R. Wasson, W. E. Halfeld, and E. V. Brown, *Inorg. Chem.* **15**, 916 (1976).

IX. Medicinal Uses of Naphthyridines

A large number of 4-oxo derivatives of the 1,8-naphthyridine ring system have been synthesized and screened for their antibacterial activity. In general, the active compounds are similar to the 1,5-naphthyridine derivative nalidixic acid.¹¹⁴⁻¹¹⁷

The following 7-substituted compounds have shown some antibacterial activity¹¹⁸⁻¹²²:



Other 1,8-naphthyridines have demonstrated antithrombic activity (**162**)¹²³ and tranquilizer, muscle relaxant, and hypnotic properties (**163**),¹²⁴ as well as anticonvulsant behavior (**163**¹²⁴ and **164**¹²⁵). Some other derivatives (**165**)

¹¹⁴ S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I. Tonetti, *Farmaco, Ed. Sci.* **28**, 722 (1973).

¹¹⁵ S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I. Tonetti, *Farmaco, Ed. Sci.* **30**, 185 (1975).

¹¹⁶ E. M. Hawes, K. W. Hindmarsh, N. W. Hamon, and B. J. A. Parkes, *Can. J. Pharm. Sci.* **10**, 45 (1975).

¹¹⁷ C. Cotel, C. Crisan, C. Jeanmart, and M. N. Messer, U.S. Patent 4,220,646 (1976).

¹¹⁸ S. Nishigaki, N. Mizushima, and K. Senga, *Chem. Pharm. Bull.* **24**, 1658 (1976).

¹¹⁹ S. Nishigaki, M. Ichiba, S. Fukazawa, M. Kanahori, K. Shinomura, F. Yoneda, and K. Senga, *Chem. Pharm. Bull.* **23**, 3170 (1975).

¹²⁰ Dainippon Pharmaceutical Co. Ltd., *Jpn. Kokai Tokkyo Koho* **81** 46,811 (1981).

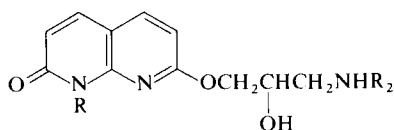
¹²¹ Dainippon Pharmaceutical Co. Ltd., *Jpn. Kokai Tokkyo Koho* **81** 05,484 (1981) [*CA* **95**, 43143 (1981)].

¹²² Dainippon Pharmaceutical Co. Ltd., *Jpn. Kokai Tokkyo Koho* **81** 05,485 (1981) [*CA* **95**, 43144 (1981)].

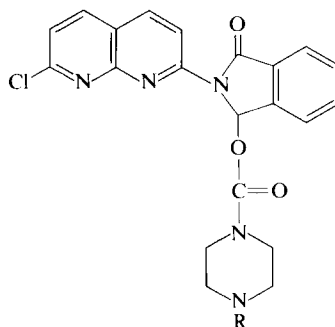
¹²³ I. Tonetti, D. Bertini, P. L. Ferrarini, O. Livi, and M. Del Tacca, *Farmaco, Ed. Sci.* **31**, 175 (1976).

¹²⁴ Chinese Academy of Medical Sciences, Shanghai, *Yao Hsueh Hsueh Pao* **15**, 630 (1980).

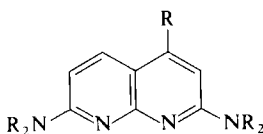
¹²⁵ S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I. Tonetti, *Farmaco, Ed. Sci.* **30**, 237 (1975).



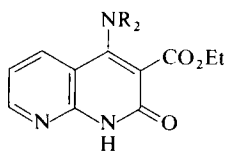
(162)



(163)

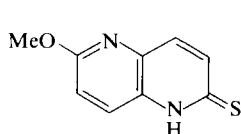


(164)

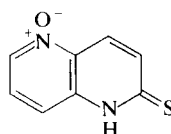


(165)

have the property of inhibiting secretion of acid stomach.¹²⁶ A number of 4-amino-substituted 1,5-naphthyridines have been shown to have no significant antimalarial activity.¹²⁷ Derivatives **166** and **167**, however, have some antitubercular and antidyentery activity.¹²⁸



(166)



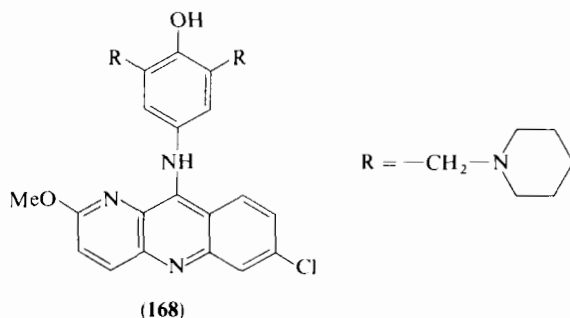
(167)

The benzo-1,5-naphthyridine (**168**) has shown significant activity against chloroquine-resistant strains of *Plasmodium falciparum*.¹²⁴ Oxo derivatives

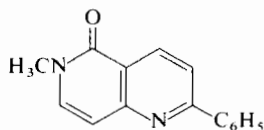
¹²⁶ A. A. Santilli and A. C. Scotese, European Patent Appl. 18,735 (1980) [CA **94**, 175095 (1981)].

¹²⁷ J. F. Pilot and E. L. Stogryn, U.S. NTIS, AD Rep. ADA023974, 49 (1975); Gov. Rep. Announce. Index (U.S.) **76**, 66 (1976).

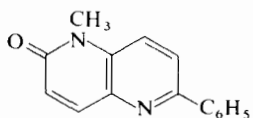
¹²⁸ R. M. Titkova, A. S. Elina, E. N. Padeiskaya, and L. M. Polukhina, Khim. Farm. Zh. **9**, 10 (1975).



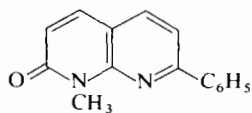
169, **170**, and **171** have some insecticidal activity against *Nephotethix*



(169)

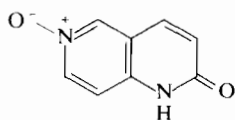


(170)

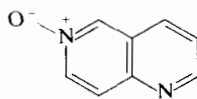


(171)

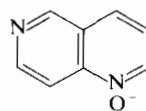
cincticeps and *Musea demostica*.¹²⁹ *N*-oxides **172**, **173** and **174** have some



(172)

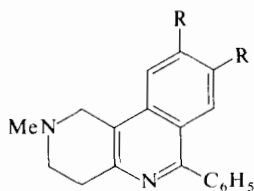


(173)



(174)

general antibacterial activity.¹³⁰ In combination with β -blocking agents, the tetrahydro-1,6-naphthyridine (**175**) has some curative power in cardiac insufficiencies and infarction.¹³¹



(175)

¹²⁹ I. Takeuchi and Y. Hamada, *Chem. Pharm. Bull.* **24**, 1813 (1976).

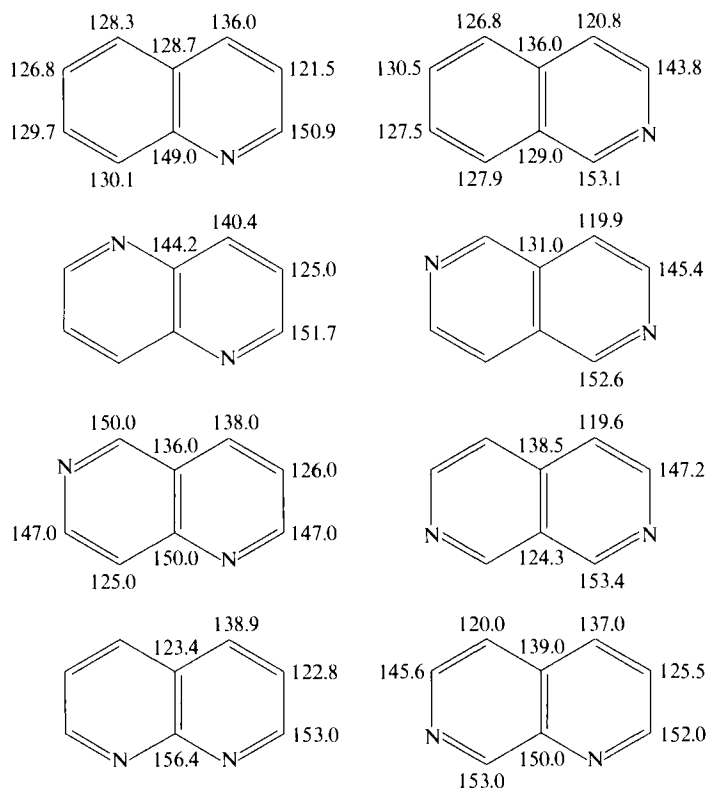
¹³⁰ T. Takahasi, Y. Hamada, I. Takeuchi, and H. Uchiyama, *Yakugaku Zasshi* **89**, 1260 (1969).

¹³¹ A. G. Sandox, *Jpn. Kokai Tokkyo Koho* **80/85**, 519 (1980).

X. Spectroscopic Properties

A. NUCLEAR MAGNETIC RESONANCE SPECTRA

The proton NMR spectra for the various naphthyridines have already been listed in Volume 2 of this series.¹ The ¹³C spectra either have since been reported or have since been obtained in the authors' laboratory.^{132,133} The data, along with the ¹³C chemical shifts for quinoline and isoquinoline, are as follows (δ ppm, with respect to TMS at 0 ppm):



These chemical shifts are linearly dependent upon the total charge density on the carbons as calculated by self-consistent molecular orbital approximations.

¹³² A. C. Boicelli, R. Daniel, A. Mangini, L. Lunazzi, and G. Placucci, *J. C. S. Perkin II*, 1024 (1973).

¹³³ The data for the 1,6- and 1,7-naphthyridines were obtained in the author's laboratory in saturated CH₃CN solution with TMS as an external reference.

The $^1\text{H-NMR}$ spectra of some of the naphthyridines¹³⁴⁻¹³⁶ partially oriented in liquid crystalline solvents have been obtained. Except in 1,8-naphthyridine, in which X-ray diffraction analysis has shown that the two rings are not totally coplanar, the naphthyridines have a hydrogen-to-hydrogen ratio identical to that of the corresponding hydrogens in pyridine. Thus, "fusion" of the pyridine rings to generate these naphthyridines does not affect the bond distances significantly.

B. VIBRATIONAL SPECTRA

The use of infrared and Raman spectra of 1,6- and 1,8-naphthyridine has allowed the assignment of all 42 fundamental vibrations of these two ring systems.¹³⁷ A transferable valence force field has been developed and applied to the calculation of the out-of-plane vibrations of 1,5-, 1,6-, 1,7-, 1,8-, and 2,7-naphthyridines.¹³⁸

C. PHOTOELECTRON SPECTRA

The high-resolution Me 584 ϕ photoelectron spectra of all of the naphthyridines have been reported.¹³⁹ In the 1,5- and 1,8-naphthyridines, the first ionization involves an n -orbital, whereas in the other naphthyridines the π -orbital is involved. The observed potentials (eV) for n - and π -orbitals are

1,5-naphthyridine:	n : 9.20, 10.40, 1.20 π : 11.05
1,6-naphthyridine:	n : 9.50, 9.90, 0.40 π : 9.07, 11.10
1,7-naphthyridine:	n : 9.30, 10.00, 0.70 π : 8.99, 11.14
1,8-naphthyridine:	n : 9.20, 10.10, 0.90 π : 11.33
2,6-naphthyridine:	n : 9.40, 10.00, 0.60 π : 8.87
2,7-naphthyridine:	n : 9.35, 10.10, 0.75 π : 8.98

¹³⁴ C. L. Khetrapal and A. C. Kunwar, *Mol. Cryst. Liq. Cryst.* **15**, 363 (1972).

¹³⁵ C. L. Khetrapal, A. Saupe, and A. C. Kunwar, *Mol. Cryst. Liq. Cryst.* **17**, 121 (1972).

¹³⁶ R. Daniel, L. Lunazzi, and C. A. Veracini, *J. C. S. Perkin II*, 19 (1976).

¹³⁷ J. T. Carrano and S. C. Wait, Jr., *J. Mol. Spectrosc.* **46**, 401 (1973).

¹³⁸ P. J. Chappell and J. G. Ross, *J. Mol. Spectrosc.* **83**, 192 (1977).

¹³⁹ D. M. W. Van den Ham and D. Van der Meer, *Chem. Phys. Lett.* **447** (1972).

D. OTHER SPECTRAL DATA

The polarized phosphorescence spectra of 1,5-naphthyridine and its d_6 isomer in durene and in durene- d_{14} mixed crystals have been obtained at 4°K. The lowest singlet state is at 27123 and 27200 cm^{-1} , whereas the corresponding triplet state is at 23215 and 23288 cm^{-1} for the proto and deutero compounds, respectively. The phosphorescence lifetime in durene crystals is 0.23 sec.¹⁴⁰ The polarized spectra (4°K) of 1,5-naphthyridine and its d_6 isomer in naphthalene have also been examined. There is a difference between the spectra in naphthalene and in durene attributable to a decrease in the strong vibronic coupling that is considered to exist between the $n \rightarrow \pi^*$ state and the higher $\pi \rightarrow \pi^*$ states.¹⁴¹ The EPR spectrum of 1,6-naphthyridine in its lowest triplet state has been observed for solid solutions in single crystals of durene. The nuclear hyperfine structure allows an estimate of 0.14 to be made for the spin density on the nitrogen atom in the 1-position.¹⁴²

XI. Electrochemical Studies

The 1,5-, 1,6-, 1,7-, 1,8-, 2,6-, and 2,7-naphthyridines have been electrochemically reduced to afford radicals that decay by a slow shift of hydrogen from nitrogen to carbon.¹⁴³ The resulting radicals dimerize readily. In acid media the first reduction step produces a radical-cation that is relatively stable in the 1,7- and 2,6-naphthyridines, whereas in 2,7-naphthyridine, the species is stable for a few minutes only. All of these radical-cations undergo a hydrogen shift from nitrogen to carbon to form unstable radicals that react with original cation radicals to form dimers. The process is an acid- or base-catalyzed first-order reaction.¹⁴⁴

See chapter by van der Plas and co-workers, p. 95 of this volume, for a detailed discussion of these types of reactions.

¹⁴⁰ G. Fischer, *Chem. Phys. Lett.* **21**, 305 (1973).

¹⁴¹ A. D. Jordon, G. Fischer, and I. G. Ross, *J. Mol. Spectrosc.* **87**, 345 (1981).

¹⁴² R. Bramley and B. J. McCool, *Mol. Phys.* 659 (1974).

¹⁴³ L. Roullier and E. Laviron, *Electrochim. Acta*, 421 (1976).

¹⁴⁴ L. Roullier and E. Laviron, *Electrochim. Acta*, 773 (1978).

Pseudoazulenes

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I. Introduction

General points of view regarding classification of heterocyclic compounds have been developed. One starts with the hypothesis that the essential properties of the total system are unchanged by a sulfur atom, an oxygen

atom, or an NR group.¹ These ideas, developed by Robinson in 1917, have found a place among the modern ideas about heteroaromaticity.^{2,3} According to Elguero *et al.*³ a heteroaromatic compound can be defined as follows: "A monocyclic or *o*-condensed polycyclic conjugated heterocycle will be aromatic if it possesses an odd number of *p*- or π -electron doublets."

In 1957, this approach was applied for the first time simultaneously by Mayer,⁴ Boyd,⁵ and Los, Saxena, and Stafford⁶ to an extensive group of heterocyclic compounds that can be considered analogs of the aromatic hydrocarbons of the azulene series.^{7,8} To express the general relationship among these compounds, they were classified by the term "pseudoazulenes." Even then a number of such products existed,^{1,9-36} but correlations involving this classification were not made. Instead, the investigation of these compounds was predominantly stimulated by the fact that the alkaloids sempervirine, alstonine, serpentine, and cryptolepine have pseudoazulene-type structures.

Since that time many new compounds of the pseudoazulene type have been described; but there are only a few reports giving a clear review of the total field.^{2,37} Moreover, there are a number of reviews about special pseudoazulenes³⁸⁻⁴⁰ in which the overall concept of pseudoazulenes received little notice.

¹ W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **115**, 933 (1919).

² M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, **17**, 255 (1974).

³ J. Elguero, R. M. Claramunt, and A. J. H. Summer, *Adv. Heterocycl. Chem.*, **22**, 183 (1978).

⁴ R. Mayer, *Angew. Chem.*, **69**, 481 (1957).

⁵ G. V. Boyd, *Chem. Ind. (London)*, 1244 (1957).

⁶ M. Los, J. P. Saxena, and W. H. Stafford, *Proc. Chem. Soc., London*, 352 (1957).

⁷ T. Nozoe, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, 1973 Vol. 3, p. 201 (1973).

⁸ V. B. Mochalin and Yu. N. Porshnev, *Usp. Khim.*, **46**, 1002 (1977).

⁹ J. W. Armit and R. Robinson, *J. Chem. Soc.*, 827 (1922); 1604 (1925).

¹⁰ B. Fichter and D. Boehringer, *Chem. Ber.*, **39**, 3922 (1906); **40**, 3478 (1907).

¹¹ F. Angelico, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.*, **17**, 655 (1908); F. Angelico and C. Labisi, *Gazz. Chim. Ital.*, **40**, 411 (1910).

¹² W. J. Hale, *J. Am. Chem. Soc.*, **38**, 2535 (1916).

¹³ W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **115**, 933 (1919); W. O. Kermack, W. H. Perkin, and R. Robinson, *ibid.*, **121**, 1872 (1922); R. Robinson and M. Robinson, *ibid.*, **125**, 827 (1925); V. V. S. Iyer and R. Robinson, *ibid.*, 1636 (1934).

¹⁴ J. W. Armit and R. Robinson, *J. Chem. Soc.*, **121**, 836 (1922).

¹⁵ R. Robinson and S. Thornely, *J. Chem. Soc.*, **125**, 2169 (1924).

¹⁶ V. Hasenfratz, *Ann. Chim. (Paris)*, **7**, 151 (1927).

¹⁷ W. O. Kermack and J. Slater, *J. Chem. Soc.*, 32 (1928); 789 (1928).

¹⁸ W. O. Kermack and J. F. Smith, *J. Chem. Soc.*, 1999 (1930); W. O. Kermack and N. E. Story, *ibid.*, 607 (1950).

¹⁹ R. Konovalova and A. P. Orechov, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **272**, 748 (1934).

²⁰ R. H. Freak and R. Robinson, *J. Chem. Soc.*, 2013 (1938).

II. Systems of Pseudoazulenes

A. KNOWN SYSTEMS OF PSEUDOAZULENES

The replacement principle mentioned above can be applied to the hydrocarbon azulene (**1**) in different ways (see Scheme 1):

1. Replacement of one C=C bond in the seven-membered ring by a heteroatom generates compounds of the [*b*]- and [*c*]-series (**2** and **3**)
2. Replacement of one C=C bond in the five-membered ring (**4**)
3. Replacement of two C=C bonds in the seven-membered ring (**5** or **6**; here system **6** must be a zwitterion)
4. Replacement of one C=C bond in the seven- and five-membered rings
5. Replacement of two C=C bonds in the seven-membered ring and of one C=C bond in the five-membered ring (**7**, **8**, or **9**).

These C=C bonds can be replaced by an oxygen, sulfur, selenium, or tellurium atom or by an NR group. The number of possible systems is considerably increased by multiple substitutions.

Benzocondensed azulenes can be treated in the same way. Correspondingly, numerous pseudoazulenes can be constructed from azaazulenes or

²¹ N. J. Leonard and R. C. Elderfield, *J. Org. Chem.* **7**, 556 (1942); R. C. Elderfield and A. P. Gray, *ibid.* **16**, 506 (1951).

²² V. Prelog, *Helv. Chim. Acta* **31**, 588 (1948).

²³ S. J. Holt and V. Petrov, *J. Chem. Soc.*, 919 (1948).

²⁴ R. B. Woodward and B. Witkop, *J. Am. Chem. Soc.* **71**, 379 (1949).

²⁵ R. Bentley and T. S. Stevens, *Nature (London)* **164**, 141 (1949).

²⁶ O. E. Edwards and L. Marion, *J. Am. Chem. Soc.* **71**, 379 (1949).

²⁷ R. Speitel and E. Schlittler, *Helv. Chim. Acta* **32**, 860 (1949); E. Schlittler and H. Schwarz, *ibid.* **33**, 1463 (1950); **34**, 629 (1951).

²⁸ H. Schwarz, *Experientia* **6**, 330 (1950).

²⁹ J. W. Cook, J. D. London, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

³⁰ E. Gellert, Raymond-Hamet, and E. Schlittler, *Helv. Chim. Acta* **34**, 642 (1951).

³¹ R. H. Glauert and F. G. Mann, *J. Chem. Soc.*, 2135 (1952).

³² B. Witkop, *J. Am. Chem. Soc.* **75**, 3361 (1953).

³³ A. P. Gray, E. E. Spinner, and C. J. Caralitto, *J. Am. Chem. Soc.* **76**, 2792 (1954).

³⁴ P. Karrer and H. Schmid, *Angew. Chem.* **67**, 361 (1955).

³⁵ A. P. Gray, *J. Am. Chem. Soc.* **77**, 5930 (1955).

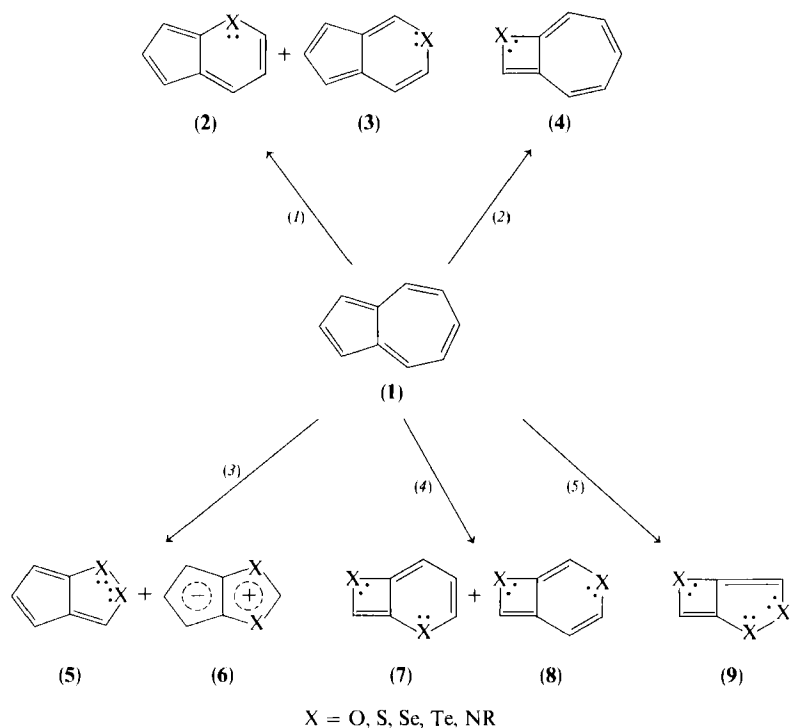
³⁶ I. P. Spenser, *J. Chem. Soc.*, 3659 (1956).

³⁷ H.-J. Timpe and A. V. El'tsov, *Z. Chem.* **15**, 172 (1975).

³⁸ F. Freemann, *Adv. Heterocycl. Chem.* **15**, 187 (1973).

³⁹ M. A. Khan and J. F. da Rocha, *Heterocycles*, 1059 (1978).

⁴⁰ L. N. Achontov and A. A. Prokopov, *Usp. Khim.* **49**, 814 (1980).



SCHEME 1

polyazaazulenes. Scheme 2 summarizes the hypothetical systems (11–20) resulting from 4-azaazulene (10). Zwitterionic systems are not taken into consideration. Because of the large number of azaazulene structures,⁴¹ the number of pseudoazulenes is particularly high. The 4- and 6-substituted purines (21 and 22) are also grouped with them. They are not discussed here because they have been considered in other work,⁴² but without mention of their relationship to the pseudoazulenes.

Another peculiarity appears in the case of replacement by an NR group: it can be introduced into the carbon skeleton in such a way that it links both ring systems. Structures of this type, e.g., indolizine (23),⁴³ quinolizine (24),⁴⁴ and some azapentalenes³ (such as 25),⁴⁵ are pseudoazulenes, also,

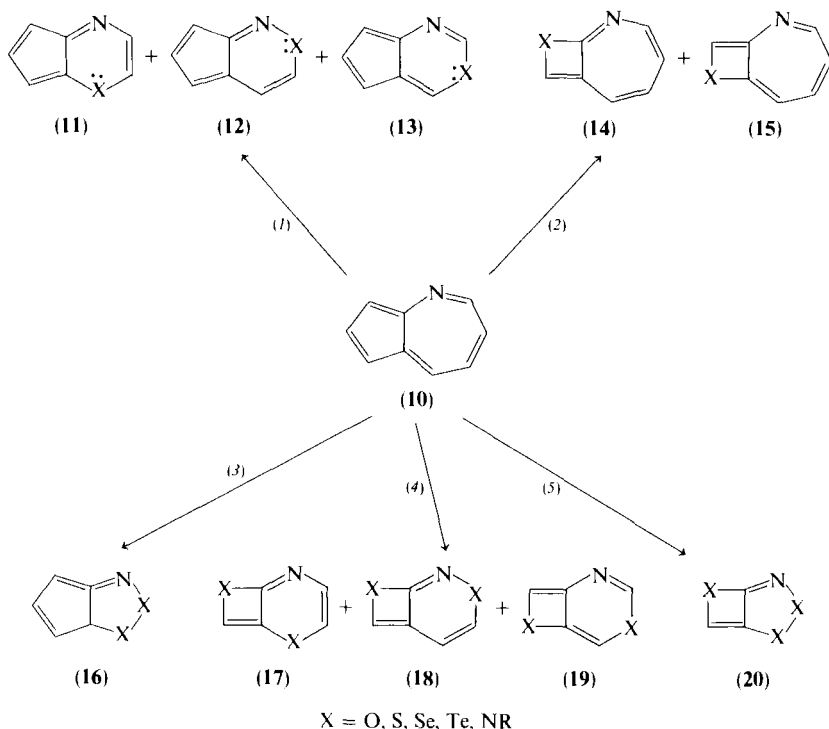
⁴¹ K. Hafner, *J. Heterocycl. Chem.*, **Suppl.** 3, 33 (1975).

⁴² J. H. Lister, *Adv. Heterocycl. Chem.* **24**, 215 (1979).

⁴³ F. J. Swinbourne, J. H. Hunt, and G. Klinkert, *Adv. Heterocycl. Chem.* **23**, 103 (1978).

⁴⁴ W. L. Mosby, *Chem. Heterocycl. Comp. (Engl. Transl.)* **15**, 117 (1961).

⁴⁵ V. K. Kibirev and F. S. Babichev, *Ukr. Khim. Zh.* **30**, 488 (1964).



SCHEME 2

according to the above definition. These are also not discussed in the present paper because reviews are available.

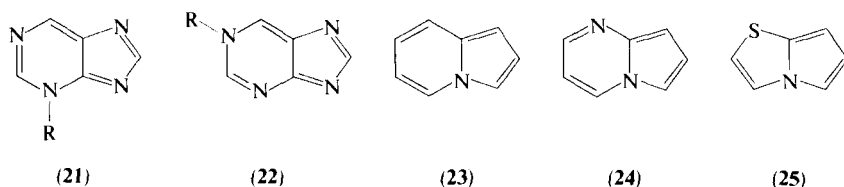
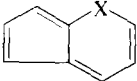
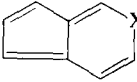
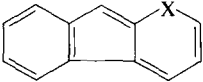
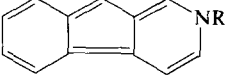
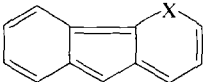
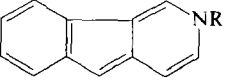
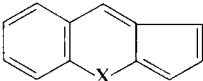
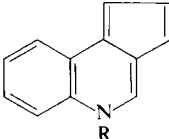
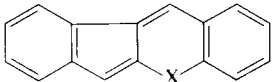
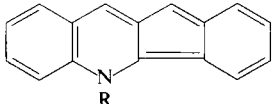
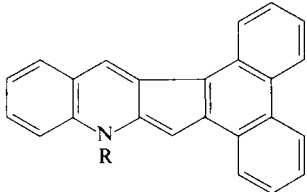


Table I, containing compounds **26–87**, summarizes all pseudoazulenes known through July 1979, as well as the corresponding literature. Not included are hydroderivatives of known and hitherto unknown pseudoazulene systems containing many oxo and thio compounds. Such pseudoazulenes are predominantly of the type produced by introduction of an NR group. Only one system (**78**) of pseudoazulenes containing a selenium group is known, whereas tellurium compounds are unknown because of difficulties

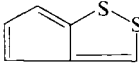
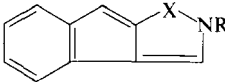
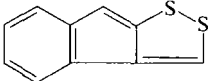
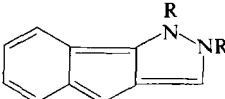
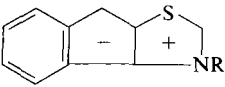
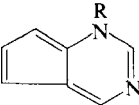
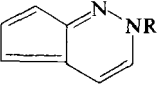
TABLE I
KNOWN PSEUDOAZULENE SYSTEMS

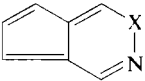
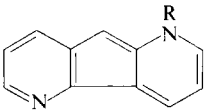
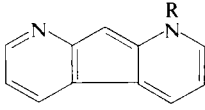
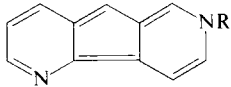
Structure	No.	X	Nomenclature	References
	26	NR	1 <i>H</i> -Pyrindine	38, 50–67
	27	O	Cyclopenta[<i>b</i>]pyran	5, 50, 51, 60, 61, 67–74
	28	S	Cyclopenta[<i>b</i>]thiopyran	4, 60, 61, 67, 75–82
	29	NR	2 <i>H</i> -Pyrindine	61, 63, 64, 66, 67, 83–87
	30	O	Cyclopenta[<i>c</i>]pyran	61, 67, 83
	31	S	Cyclopenta[<i>c</i>]thiopyran	61, 67, 79, 80, 84–86, 46, 88–91
	32	NR	1 <i>H</i> -Indeno[2,1- <i>b</i>]pyridine	38, 57, 92–95
	33	O	Indeno[2,1- <i>b</i>]pyran	96–102
	34	S	Indeno[2,1- <i>b</i>]thiopyran	75, 78
	35		2 <i>H</i> -Indeno[2,1- <i>c</i>]pyridine	103–106
	36	NR	1 <i>H</i> -Indeno[1,2- <i>b</i>]pyridine	92, 103, 105, 107
	37	S	Indeno[1,2- <i>b</i>]thiopyran	75, 107
	38		2 <i>H</i> -Indeno[1,2- <i>c</i>]pyridine	94

	39	NR	4 <i>H</i> -Cyclopenta[<i>b</i>]quinoline	6, 38, 50, 51, 57, 49, 60, 106, 108–115
	40	O	Cyclopenta[<i>b</i>][1]benzopyran	50, 51, 68, 69, 70, 73, 48, 76, 102, 110, 116–121
	41	S	Cyclopenta[<i>b</i>][1]benzothiopyran	46, 60, 75, 110, 48, 122
	42		5 <i>H</i> -Cyclopenta[<i>c</i>]quinoline	115, 123
	43	NR	5 <i>H</i> -Indeno[2,1- <i>b</i>]quinoline	13, 39, 57, 60, 101, 106, 110, 124–126
	44	O	Indeno[2,1- <i>b</i>][1]benzopyran	60, 69, 70, 76, 101, 102, 110, 116, 117, 126–130
	45	S	Indeno[2,1- <i>b</i>][1]benzothiopyran	46, 60, 75, 110, 131
	46		5 <i>H</i> -Indeno[1,2- <i>b</i>]quinoline	9
	47		10 <i>H</i> -Dibenz[4,5:6,7]indeno[2,1- <i>b</i>]quinoline	132

(continued)

TABLE I (continued)

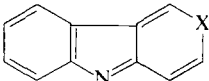
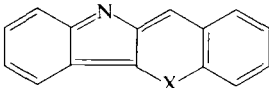
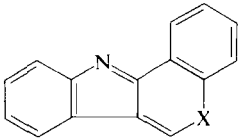
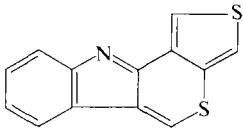
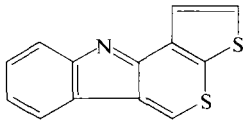
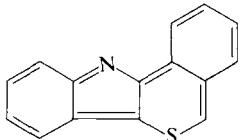
Structure	No.	X	Nomenclature	References
	48		Cyclopenta-1,2-dithiole	46, 133
	49 50	NR O	1,2 <i>H</i> -Indeno[2,1- <i>c</i>]pyrazole Indeno[2,1- <i>c</i>]isoxazole	3, 134–136 135
	51		Indeno[2,1- <i>c</i>]1,2-dithiole	137
	52		1,2 <i>H</i> -Indeno[1,2- <i>c</i>]pyrazole	135
	53		Indeno[1,2- <i>a</i>]thiazoliumbe- tain	134
	54		1 <i>H</i> -Cyclopenta[<i>e</i>]pyrimidine	61, 138, 139
	55		2 <i>H</i> -Cyclopenta[<i>c</i>]pyridazine	140–142

	56	NR	2 <i>H</i> -Cyclopenta[<i>d</i>]pyridazine	12, 61, 66, 138, 139, 143–155
	57	O	Cyclopenta[<i>d</i>]1,2-oxazine	61
	58		1 <i>H</i> -Cyclopenta[1,2- <i>b</i> :3,4- <i>b'</i>]-dipyridine	92
	59		1 <i>H</i> -Cyclopenta[1,2- <i>b</i> :4,3- <i>b'</i>]-dipyridine	92
	60		1 <i>H</i> -Cyclopenta[2,1- <i>b</i> :3,4- <i>b'</i>]-dipyridine	92
	61		2 <i>H</i> -Cyclopenta[1,2- <i>c</i> :3,4- <i>b'</i>]-dipyridine	92
	62	NR	4 <i>H</i> -Cyclopenta[<i>b</i>]quinoxaline	156–158
	63	O	Cyclopenta[<i>b</i>]1,4-benzoxazine	159
	64	S	Cyclopenta[<i>b</i>]1,4-benzothiazine	160–162

(continued)

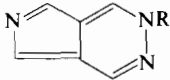
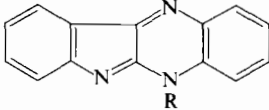
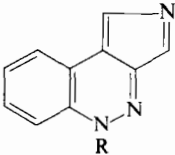
TABLE 1 (continued)

Structure	No.	X	Nomenclature	References
	65		4 <i>H</i> -Cyclopenta[<i>c</i>]cinnoline	163, 164
	66	NR	5 <i>H</i> -Indeno[1,2- <i>b</i>]quinoxaline	110
	67	S	Benzo[<i>b</i>]indeno[1,2- <i>e</i>]1,4-thiazine	110
	68		7 <i>H</i> -Pyrrolo[2,3- <i>b</i>]pyridine	62, 66, 165–172
	69	NR	1 <i>H</i> -Pyrido[2,3- <i>b</i>]indole	20, 32, 33, 35, 87, 173, 174
	70	S	Thiopyrano[2,3- <i>b</i>]indole	175
	71		1 <i>H</i> -Pyrido[3,2- <i>b</i>]indole	31, 176
	72		2 <i>H</i> -Pyrido[3,4- <i>b</i>]indole	13, 15, 17, 19, 21, 22, 24, 29, 32–36, 177–184

	73	NR	2 <i>H</i> -Pyrido[4,3- <i>b</i>]indole	35, 185–187
	74	O	Pyrano[4,3- <i>b</i>]indole	188
	75	S	Thiopyrano[4,3- <i>b</i>]indole	189–191
	76	NR	5 <i>H</i> -Quindoline	10, 14, 23, 30
	77	S	1-Benzothiopyrano[3,2- <i>b</i>]-indole	192
	78	NR	5 <i>H</i> -Indolo[3,2- <i>c</i>]quinoline	18, 33
	79	O	1-Benzopyrano[4,3- <i>b</i>]indole	193
	80	S	1-Benzothiopyrano[4,3- <i>b</i>]-indole	193–196
	81	Se	1-Benzoselenino[4,3- <i>b</i>]-indole	197
	82		Thieno[3',4':5,6]thiopyrano[4,3- <i>b</i>]indole	198
	83		Thieno[3',2':5,6]thiopyrano[4,3- <i>b</i>]indole	198
	84		2-Benzothiopyrano[4,3- <i>b</i>]-indole	193

(continued)

TABLE I (continued)

Structure	No.	X	Nomenclature	References
	85		2H-Pyrrolo[3,4-d]pyridazine	199
	86		5H-Indolo[2,3-b]quinoxaline	200-202
	87		5H-Pyrrolo[4,3-c]cinnoline	15, 203

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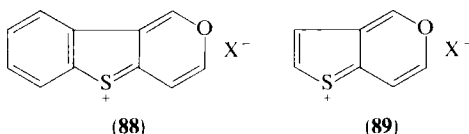
(continued)

FOOTNOTES (continued)

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in synthesis and a shortage of investigations. Pseudoazulenes having one nitrogen atom in the five-membered ring are especially numerous.

Four-membered ring systems that, according to the general principles given in Schemes 1 and 2, also belong to the pseudoazulene group have not been described. In all probability their stability is reduced by considerable ring strain. This assumption is confirmed by quantum chemical calculations on **4** ($X = S$).⁴⁶ Systems **88** and **89**,⁴⁷ which must be considered as heteronia pseudoazulenes, are not discussed in this chapter.



B. NOMENCLATURE

Originally the proposal was made to classify pseudoazulenes as follows: pseudoazulenes having a sulfur-containing group should be called thialenes,⁴ those having an oxygen-containing group, oxalenes,⁴⁸ and those having an NR group, azalenes.⁴⁹ This classification is no longer commonly used although it does express the linguistic relationship to the azulenes. In this chapter the terms *thialenes*, *oxalenes*, and *azalenes* are used when the complete group of these pseudoazulenes is referred to.

Pseudoazulenes are named according to IUPAC rules. Furthermore, there are some common aspects of nomenclature in use, e.g., pyridines for **26** and **29** and quindolines for **76**. For pyridoindoles **69**, **71**, **72**, and **73** the terms α -, β -, γ -, and δ -carbolines are often used.

The compounds summarized in Table I can easily be numbered: position 1 is always located at the upper atom of the right-hand ring next to the site of ring fusion. The numbering then proceeds continuously in a clockwise direction for all atoms that can be substituted.

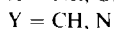
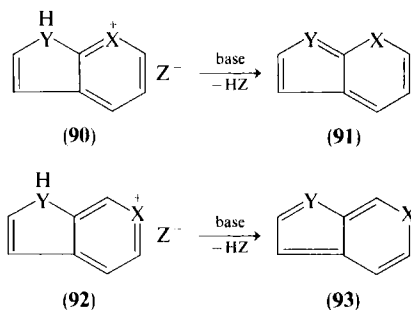
III. Synthesis of Pseudoazulenes

Considering the great variety of heterocyclic structures from which pseudoazulenes can be derived, it is hardly possible to generalize all the steps pertaining to their synthesis. The last steps, however, can be summarized, but even this classification, which is explained below in more detail, has some limitations.

A. GENERAL METHODS OF SYNTHESIS

1. Deprotonation of Quaternary Salts

Many of the pseudoazulenes summarized in Table I were prepared from the corresponding quaternary salts (**90** and **92**) by deprotonation reactions (Scheme 3). This type of synthesis is especially advantageous for azulenes and oxalenes, although thialenes are seldom prepared in this way (e.g., systems **37**,¹⁰⁷ **51**,¹³⁷ and **67**¹⁷⁶) because of the difficult synthesis of the corresponding thiopyrylium salts.²⁰⁴ However, with the exception of condensed compounds (e.g., systems **35**,^{104,105} **38**,⁹⁴ **61**,⁹² **72**,^{24-29,32-36} and **73**,^{35,185,186}), this approach also has disadvantages for the preparation of azulenes (**93**: X = NR) of the [c]-series.



SCHEME 3*

Yields of the deprotonation reactions are about 60 to 80% and are essentially dependent on the stability of the resulting pseudoazulene systems (see Section IV,A).

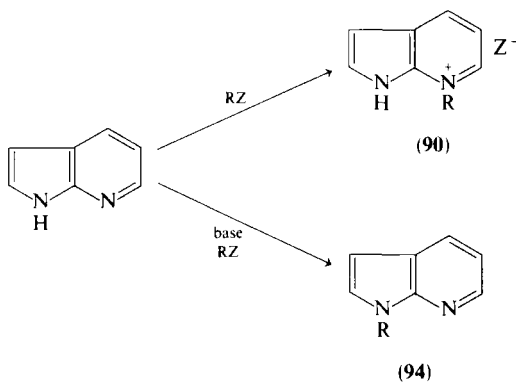
Azalene salts **90** and **92** are obtained by quaternization of the corresponding heterocyclic bases with alkyl halides or tosylates. If the heterocyclic base contains several nitrogen atoms, alkylation can produce different quaternary salts. Quaternization, however, is surprisingly selective if certain conditions are met.²⁰⁵ Pyrrolo- and indolopyridines containing one pyridine- and one pyrrole-type nitrogen atom in their molecular lattice are (in aprotic solvents) almost exclusively alkylated at the nitrogen atom of the pyridine

* In Schemes 3-6, 8-10, and 13-14 and in Eqs. (4-6) of this chapter, ring substituents are not shown.

²⁰⁴ A. T. Balaban, W. Schroth, and G. W. Fischer, *Adv. Heterocycl. Chem.* **10**, 241 (1969).

²⁰⁵ J. A. Zoltewicz and L. W. Deady, *Adv. Heterocycl. Chem.* **22**, 72 (1978).

ring by various alkylating agents such as phenacyl halide or α -halo esters.^{26,33,94,169,176,201,203} In the presence of strong bases such as sodium amide, products (94) substituted at the pyrrole nitrogen are formed^{20,165,167,183}; they are useless for the synthesis of pseudoazulenes (see Scheme 4). These rules of alkylation have been summarized by Kermack.²⁰⁶



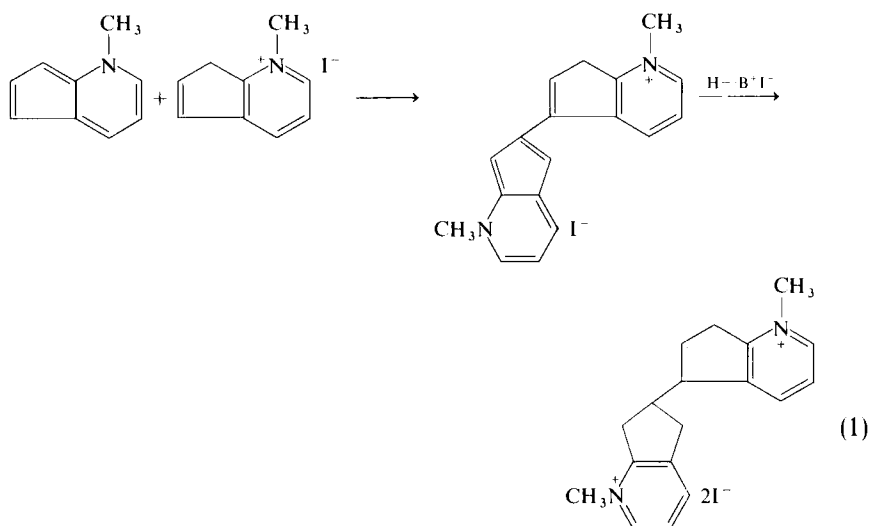
SCHEME 4

If the heterocyclic base contains several pyridine-type nitrogens select can also be observed. Indeno[1,2-*b*]quinoxalines, for example, are quaternized at the N-10 atom.¹¹⁰ The alkylation of heterocycles containing one pyrrole-type nitrogen and several pyridine-type nitrogens is apparently selective (e.g., indolo[2,3-*b*]quinoxaline).²⁰¹ The yields of quaternary salts, however, are extremely low,²⁰¹ even if phenacyl halides or α -halo ester are used.²⁰⁷ Perhaps the resultant quaternary salts are dealkylated.^{200,207}

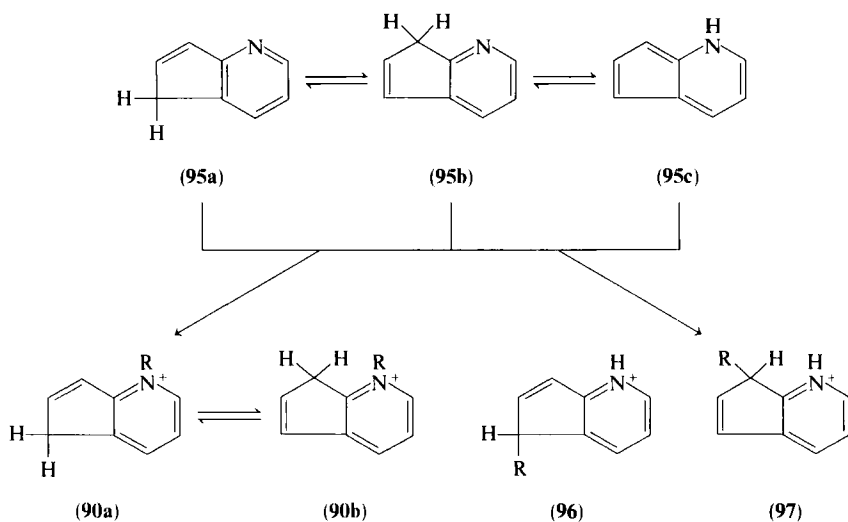
In many alkylations other side reactions can contribute to losses in yields of quaternary salts **90** and **92**. Preferably, the quaternization is carried out in aprotic solvents because in protic solvents the heterocyclic base can give rise to deprotonation of these salts (especially if $Y = CH$).^{58,59} Then, through substitution reactions the desired pseudoazulene products can be produced from substances with the quaternary salts that harden in the reaction medium (Eq. 1).

²⁰⁶ W. O. Kermack and J. E. McKail, in "Heterocyclic Chemistry" (R. C. Elderfield, ed.), Vol. 8, p. 314. Wiley, New York, 1961.

²⁰⁷ H.-J. Timpe, unpublished results (1979).



Many heterocyclic bases having a cyclopentadiene structure are sensitive to oxydation; they form dimers^{110,113} or cyclopentadienones^{51,125,132} in the presence of atmospheric oxygen. Therefore, the quaternization should be performed under an inert atmosphere. Further difficulties arise from the tautomerism of some heterocyclic bases (Scheme 5). This can lead to the

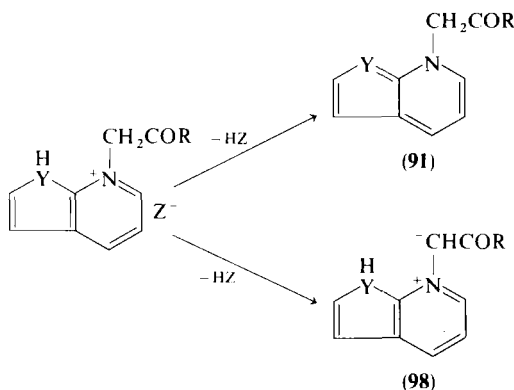


SCHEME 5

formation of quaternary salts **90**, **96**, and **97**. Qualitative investigations of 1*H*-pyrindines,^{53,58,65} cyclopenta[*b*]quinolines,¹¹² and cyclopenta[*b*]-quinoxalines^{156,157} show that in these cases the concentration of tautomers (**95c**) is about 0.01%. Moreover, the nucleophilic reactivity of the nitrogen is stronger than that of the C=C bond in **95c** and thus C-alkylation products **96** and **97** are usually formed only in trace amounts. However, **96** and **97** become the main products of the alkylation reaction if the latter is carried out in the presence of alkaline amides.^{56,112,114} The preparation of the corresponding salts (**90** and **92**) from pyrylium salts is much more complicated, as described by Balaban, Schroth, and Fischer,²⁰⁴ and will not be discussed further here. Thiopyrylium salts are in most cases obtained by condensation procedures (see Section III.A.3).

Quaternary salts **90** and **92** have an acidic CH₂ group and an acid NH proton, respectively, in their five-membered ring (see p*K*_a values in Table V); thus these compounds can easily be deprotonated. For several pyrylium salts a solvent such as water, alcohol or dimethylformamide induces deprotonation. Generally, however, dilute hydroxide or acetate bases are used.

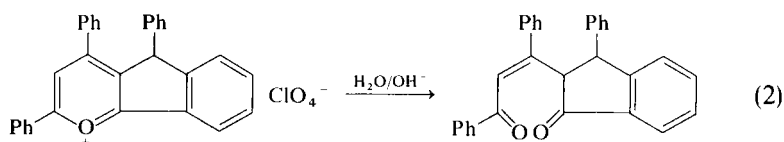
Quaternary salts (**90**) from azalenes obtained from heterocyclic bases and phenacyl halides or derivatives of α-halo carbon acids also contain an acidic exocyclic CH₂ group. Therefore, during the deprotonation, mixtures of pseudoazulenes **91** and ylides **98** can be formed, especially if Y = CH.¹⁰⁵ Quaternary salts (**90**) containing one pyrrole-type nitrogen (Y = N) deprotonate exclusively to pseudoazulenes¹⁶⁶ (Scheme 6). Analogous behavior



Y = CH, N

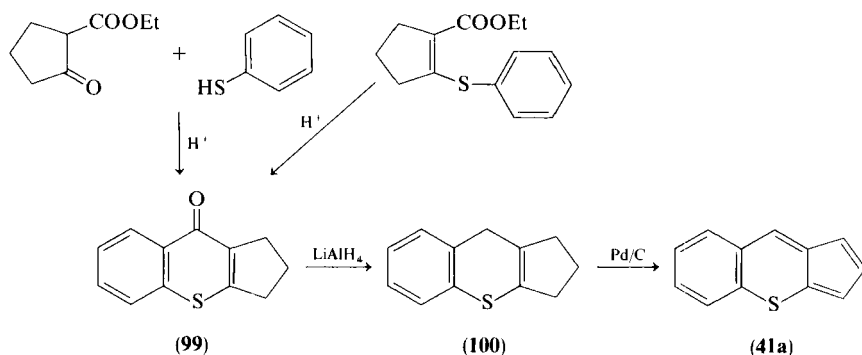
SCHEME 6

can be observed for salts (**90**: Y = CH) of the pyridine series having an exocyclic NPh group,⁵¹ whereas similar compounds of other heterocycles having a cyclopentadiene ring are not deprotonated at the five-membered ring.²⁰⁸ Some attempted deprotonation reactions to form pseudoazulenes do proceed but with complications. Benzo[*b*]indeno[2,1-*b*]pyrylium salts, for example, are not deprotonated by sodium acetate but react instead by hydrolytic ring fission (Eq. 2). Especially with pseudoazaazulenes, the deprotonation by aqueous bases results in the formation of crystal solvates. This fact has led to some misinterpretations of the structures of pseudoazulenes.^{10,14,23,30}



2. Dehydrogenation of Saturated Compounds

The synthetic approach described above assumes (particularly for azalenes) that the corresponding heteroaromatic structures or their quaternary salts are available. These compounds, which are already at maximum unsaturation, however, are sometimes made available only with difficulty, if at all



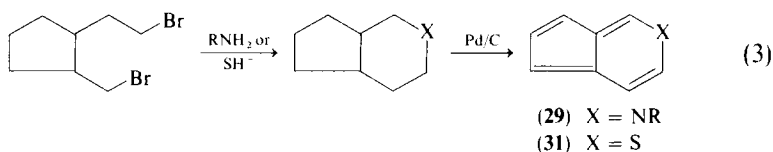
SCHEME 7

²⁰⁸ A. R. Katritzky, III, *Symp. Heterocycl.*, Kühlungsborn (1979).

(e.g., see the complicated synthesis of the pyrindanes^{52,209-211} and the cyclopenta[*b*]quinolines^{111,211,212}). In these cases it is more convenient to dehydrogenate saturated heterocyclic compounds to pseudoazulenes. The synthesis of such reduced derivatives is generally less laborious and the products are much more stable.

Numerous thialenes have been prepared by Mayer.^{4,48,77,78,122,131} The general principle of synthesis can be taken from Scheme 7, in which the synthesis of cyclopenta[*b*]-1-benzothiopyran **41** is summarized. The condensation of the cyclopentanone or the cyclopentene to **99** proceeds in good yield as does its reduction by LiAlH_4 . The limiting factor is the last step involving dehydrogenation of **100** to **41**. This dehydrogenation takes place with Pd/C catalysts in the vapor phase. Under these conditions, however, the thialenes decompose (see Section IV, A). Thus, the yields of thialenes are only about 20%. Also, *o*-allylcyclopentanthiones can be subjected to a vapor-phase dehydrogenation; they cyclize and dehydrogenate under these conditions.⁷⁸ For the preparation of azalenes and thialenes of the [c]-series (e.g., systems **29** and **30**^{85,86}) dehydrogenation by Pd catalysts is also the most convenient method.

The required hydrogenated heterocycles can easily be prepared from dihalide compounds if the principle of dilution²¹³ is observed (Eq. 3). The



dehydrogenation step is critical for the success of the procedure. The yields are generally about 25 to 30%; however, at low reactivities of the catalysts they may be only a few percent.

The application of the dehydrogenation method for the preparation of 4*H*-cyclopenta[*b*]quinolines (**39**) can be seen in Scheme 8.⁴⁹ The pseudoazulenes, however, continue to react with the chloranil. Thus, thialenes (**28**)

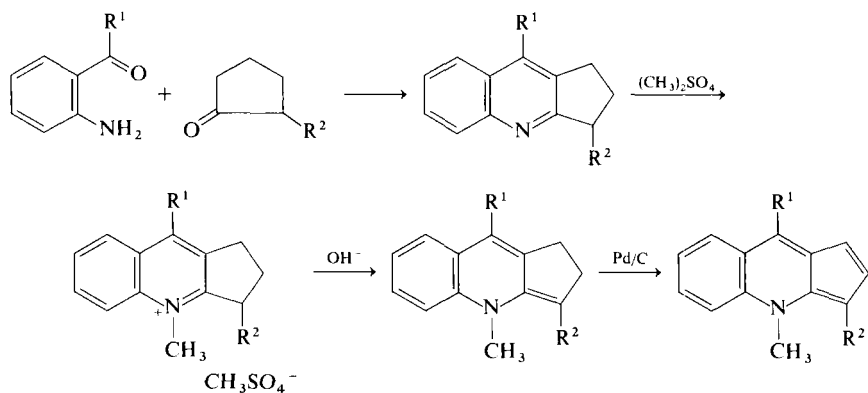
²⁰⁹ H. E. Schroeder and G. W. Rigby, *J. Am. Chem. Soc.* **71**, 2205 (1949).

²¹⁰ V. Prelog and S. Szpilfogel, *Helv. Chim. Acta* **28**, 1684 (1945).

²¹¹ R. B. Thummel and D. K. Kohli, *J. Org. Chem.* **42**, 2742 (1977).

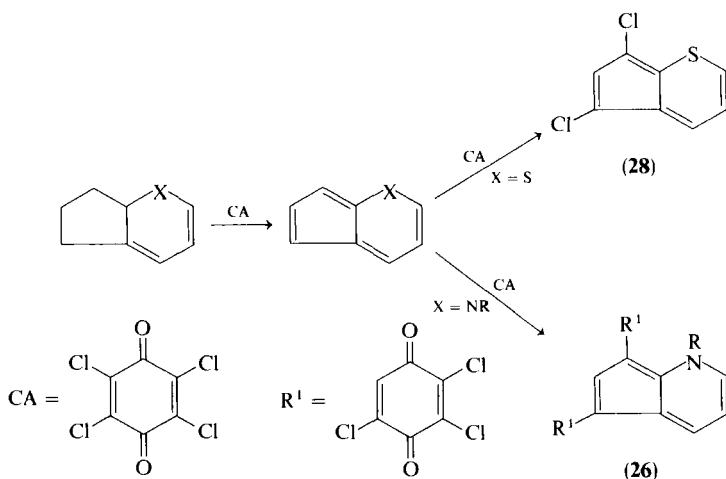
²¹² I. F. Tishchenkova, L. E. Kholodov, and V. G. Yashuskij, *Khim. Geterotsikl. Soedin.*, 102 (1971).

²¹³ F. Vögtle, J. Grütze, R. Nätscher, W. Wieder, E. Weber, and R. Grün, *Chem. Ber.* **108**, 1694 (1975).



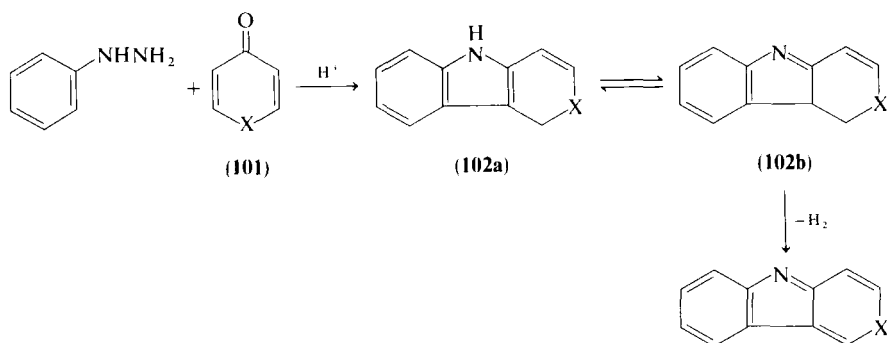
SCHEME 8

are chlorinated on the five-membered ring.^{48,77} 4*H*-cyclopenta[*b*]quinoline (39)^{109,115} and 5*H*-cyclopenta[*c*]quinolines (42)¹¹⁵ are substituted by the chloranil residue in the five-membered ring (Scheme 9; see also Section V,A).



SCHEME 9

The most representative systems of the [4,3-*b*]indolo series (75 and 79–84) are prepared by dehydrogenation of their dihydro products (Scheme 10), which can be obtained from the corresponding chromanones, thiochromanones or seleninochromanones, and aryl hydrazines by Fischer's indol



X = O, S, Se

SCHEME 10

synthesis. Sometimes the yields of the indolization step are extremely low due to the instability of certain chromanones (**101**). Surprisingly, this variation has not been applied to 1-substituted 4-pyridinones (**101**: X = NR). Sometimes dehydrogenation of the dihydro products (**102**) occurs spontaneously during melting in air. For a preparative dehydrogenation it is best to use picric acid,^{193,195,198} dicyanodichlorobenzoquinone,^{189,190,196} chloranil,¹⁸⁹ or a photochemical dehydrogenation in the presence of atmospheric oxygen.¹⁹³ For example, 1-benzothiopyrano[4,3-*b*]indoles (**80**)¹⁹³ were formed from indolenine tautomers (**102b**) by dehydrogenation. Dihydro products (**102**) that can not be tautomerized (**102a** \rightleftharpoons **102b**) are not able to be dehydrogenated to pseudoazulenes. In the case of dehydrogenation by picric acid, the picrates of the pseudoazulenes are decomposed by reaction with ammonia or by chromatography on alumina. The good yields are probably due to the formation of thermally stable pseudoazulene picrates. The yields from photochemical dehydrogenations are very low apparently due to the photoinduced decomposition of the pseudoazulene products. Reactions of this nature can be observed for numerous other pseudoazulenes.^{50,214} In the case of **79** and **84**, low yields are obtained throughout the whole preparation procedure.

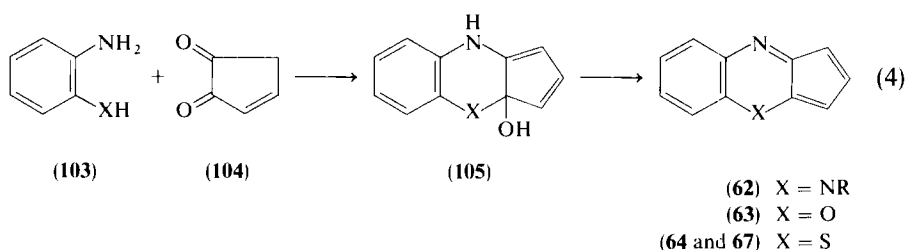
3. Methods of Condensation

Both methods explained above start from a molecular lattice already having the structure of the corresponding pseudoazulene system. The essential last step of a pseudoazulene synthesis, however, can also be to create

²¹⁴ H.-J. Timpe and B. Theiler, unpublished results (1980).

this molecular lattice by condensation. The reactants can be of very different natures depending upon the actual pseudoazulene system. Therefore, a general reaction scheme cannot be given. The following examples, however, demonstrate the principles of such syntheses.

In some condensation reactions the five-membered fragment is functionalized so that the condensation reaction with a suitable partner results directly in a pseudoazulene system. For this purpose, cyclopentendiones (**104**) are especially useful. They condense with *o*-substituted anilines (**103**) on heating in pyridine; the primary condensation product (**105**) immediately gives the pseudoazulene product by elimination of H_2O (Eq. 4).¹⁵⁸⁻¹⁶² The

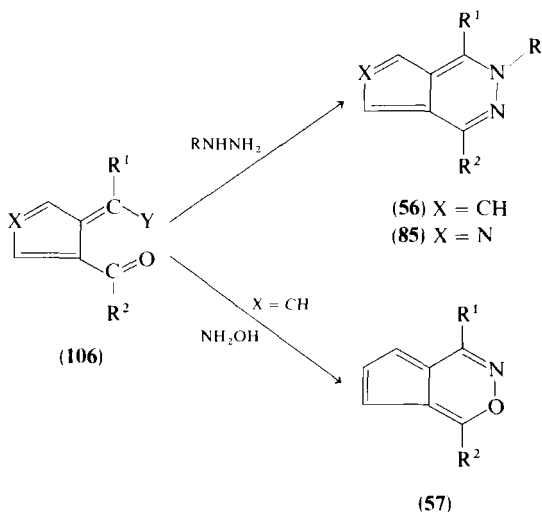


condensation reaction can also take place in acid giving good yields of pseudoazulene salts from which free bases are obtained by the action of ammonia. By analogy, pseudoazulenes of 5*H*-indolo[2,3-*b*]quinoline (**86**) can be produced.^{200-202,215}

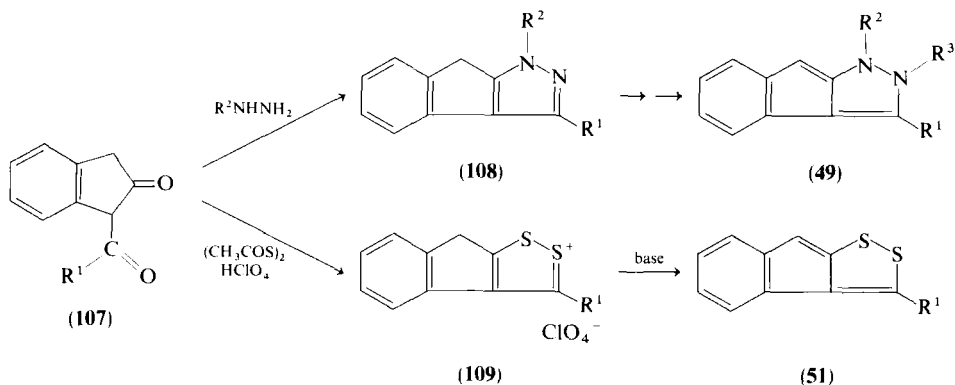
For pseudoazulene systems containing one $\text{X}-\text{Y}$ bond in the molecule, the condensation of hydrazine^{12,138,139,144-150,153,199} or hydroxylamine^{138,145} with five-membered dicarbonyl compounds or their heterocyclic products¹⁹⁹ (**106**) is the most effective method of preparation (Scheme 11). The condensation reaction gives very high yields, but the preparation of the reactants (**106**) is often complicated. For the preparation of pseudoazulene systems **5** and **6** formed by exchange of two $\text{C}=\text{C}$ bonds of the seven-membered ring in azulene (Scheme 1), five-membered dicarbonyl compounds of type **107** are used. Their reaction with alkyl or aryl hydrazines gives heterocyclic bases (**108**), which can be transformed to the pseudoazulene system (**49**) by alkylation and deprotonation (see Section III.A.1).¹³⁶

A condensation reaction with diacetyl sulfide in perchloric-acetic acid solution gives quaternary salts (**109**) that can be deprotonated to **51** (Scheme 12).¹³⁷

²¹⁵ F. D. Popp, *J. Heterocycl. Chem.* **6**, 125 (1969).

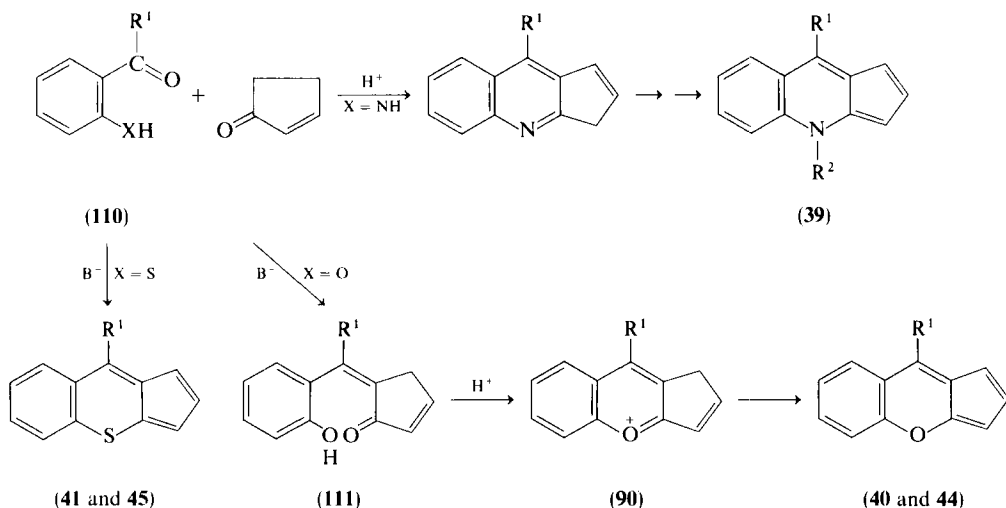


SCHEME 11



SCHEME 12

Cyclopentenones can also be used for condensation, with *o*-substituted aldehydes or ketones (110) serving as reaction partners (Scheme 13). In this way thialenes **41** and **45**, which have sulfur directly bonded to an aromatic ring, can be produced in one step by base-catalyzed condensation from *o*-mercaptobenzaldehyde and from α,β -unsaturated cyclopentenones.^{110,131} Under the same conditions salicylic aldehyde gives only open-chained products (111).^{5,72,73,99,116,127,128} Mineral acids are required for further condensation. Thereby, pyrylium salts (**90**: $Y = CH$, $X = O$) are produced, from which oxalenes are formed by deprotonation (see Section III.A.1).



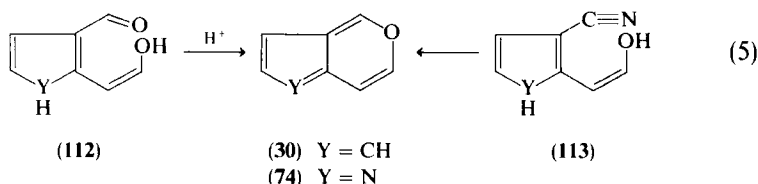
SCHEME 13

Nothing is known about analogous condensation reactions of *o*-alkylaminobenzaldehydes with α,β -unsaturated cyclopentenones leading to pseudoazulenes **39**, **43**, or **46**. Acid-catalyzed reaction of *o*-aminobenzaldehyde with cyclopentenones produces 3*H*-cyclopenta[*b*]quinolines that can be transformed to 4*H*-cyclopenta[*b*]quinolines by quaternization and subsequent deprotonation.⁵¹

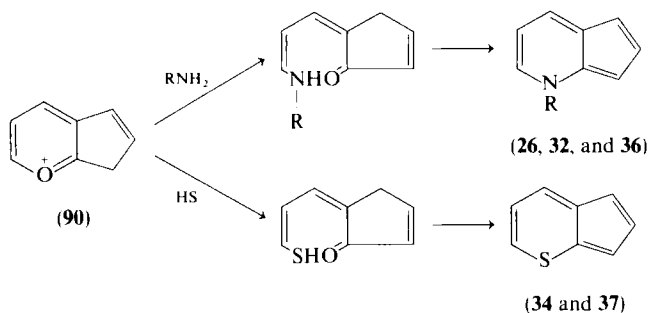
The same principle (i.e., condensation to form a six-membered ring containing heteroatoms) is realized in the formation of the thiopyrano[2,3-*b*]indole lattice from α -mercaptoindole and 1,3-diketones.¹⁷⁵

The functionalization of the five-membered ring can be promoted so that an intramolecular condensation to form the corresponding pseudoazulene becomes possible. The synthesis of compounds substituted in this way, however, is often difficult.

A pyran cyclization is possible, for example, in δ -dicarbonyl compounds (112)⁸³ or in ketonitriles (113)¹⁸⁸ (Eq. 5). The yields of these condensations are low (about 2%), probably due to the instability of the pseudoazulene

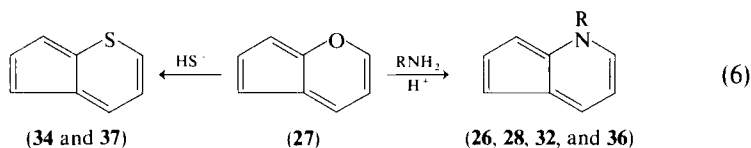


product. A similar principle is utilized in the synthesis of azalenes of type **32**⁹³ and in the preparation of pyrindines **26**.⁵⁵



SCHEME 14

The preparation of highly functionalized cyclopentadiene derivatives may be achieved by using oxalenes or their pyrylium salts (**90** and **92**, respectively), (see Scheme 14, where X = O). In this way, azalenes **26**,⁵¹ **29**,^{82,88} **32**,⁵¹ or **36**⁵¹ can be obtained by heating salts (**90**) with primary amines in dimethylformamide (Eq. 6). The reaction with sodium hydrogen sulfide gives thialenes



34 and **37**.¹⁰⁷ Oxalenes having the oxygen directly bonded to a benzene ring (e.g., **40**) cannot be transformed to azalenes in this way as expected.⁵¹

B. SPECIFIC METHODS OF SYNTHESIS

In addition to the general methods of preparation already described, there are some methods that hitherto have not been extended to a large number of pseudoazulenes.

By application of the analogy principle regarding azulene and pseudoazulene, preparations for pseudoazulenes can be found. By analogy to

Hafner's synthesis of azulene,²¹⁶ the cyclopentadienyl anion can also be used to introduce the five-membered fragment. This anion reacts with heterocyclic quaternary salts in a complex manner; the pseudoazulene, however, is obtained in one step. The total yields are only about 10%, but it is possible to use starting materials that are easily available in large quantities. This variant was applied to prepare 2*H*-cyclopenta[*d*]pyridazines (**56**) using thiadiazolium salts¹⁴⁵ and cyclopenta[*c*]thiopyranes (**31**) using *N*-methyl thiazoliumbromide.⁹⁰

The preparation of system **57** from cyclopentadienyl anion and *s*-tetrazines^{151,154} and the synthesis of the same system from fulvenes and *s*-tetrazines¹⁴³ are based on a similar principle. By its nature, the preparation of 4*H*-cyclopenta[*c*]cinnolines (**68**) from nickelocene and *o*-dihalo-benzenes¹⁶³ is analogous.

Cycloaddition reactions can also lead to the formation of pseudoazulene lattices, for example, the reaction of acetylene dicarboxylates with diazo-cyclopentadienes cyclopenta[*c*]pyridazines (**55**).¹⁴⁰⁻¹⁴²

A 1,3-dipolar cycloaddition of indanoneenamines and nitrilimines produces the indeno[2,1-*c*]pyrazole (**52**).¹³⁵ The yields of such cyclization reactions are high (60-80%). Reactions of *N*-alkylpyridine-3-ylides with picryl chloride involving cyclization give a mixture of pseudoazulenes **35** and **36**.¹⁰³ An additional preparation of pyridine **26** is from 1,2- and 1,4-oxides of azonine.⁵⁵

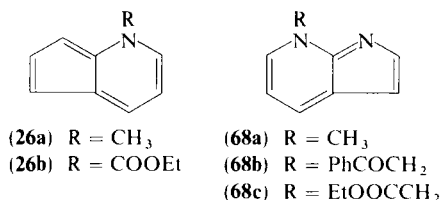
IV. Physicochemical Properties

A. GENERAL STABILITY OF PSEUDOAZULENES

The essential requirement for an exact determination of the physicochemical properties of a compound is its stability under the conditions of measurement. Thus, pseudoazulenes are difficult to measure because they are rather unstable in comparison to most azulenes. The simplest unsubstituted representatives of some systems are so thermally unstable that it is nearly impossible to isolate them. Phenyl substituents have a stabilizing effect, so polyaryl-substituted compounds can be kept at room temperature for some months without decomposing noticeably. An especially strong stabilizing effect is given by the picryl group.¹⁰⁶

In azulenes the substituent at the nitrogen atom has a very strong influence on the general stability of the compounds. Apparently, acceptor substituents

²¹⁶ K. Hafner, *Angew. Chem.* **67**, 301 (1955); K. Hafner and H. Kaiser, *Justus Liebigs Ann. Chem.* **618**, 140 (1958).



have a strong stabilizing effect, as was observed in **26**^{55,56} and **68**.¹⁶⁶ In comparison to the corresponding NCH₃ compounds pseudoazulenes **26b**, **68b**, and **68c** are much more stable. Generally, the pseudoazulenes of the [*c*]-series are more stable than those of the [*b*]-series. Stability often strongly decreases from azulenes and thialenes to oxalenes. The basic structures of 1*H*-pyridines (**26**) and cyclopenta[*b*]thiopyran (**28**) have already been synthesized, whereas cyclopenta[*b*]pyran could not be synthesized despite numerous attempts. Pseudoazaazulenes are essentially more stable than the corresponding carbocyclic compounds.⁹²

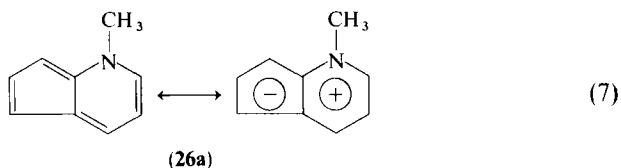
Under the influence of air, oxygen, and light numerous pseudoazulenes decompose very quickly (see Section V,E). Solutions of pseudoazulenes in aprotic solvents (particularly *n*-hexane and benzene) can often be stored for long periods. Nearly all compounds decompose in protic solvents within a short time.

Azulenes are stable to acids or bases. Most pseudoazulenes, however, decompose in acidic or alkaline media. Some compounds dissolve in strong acids without decomposition (see Section V,C), on dilution with water or aqueous bases, however, only polymeric products can be isolated.⁸⁶ Even in these cases phenyl substituents have a stabilizing effect: after heating for 5–10 min in concentrated or semiconcentrated acids, polyaryl-substituted pyridines (**26**) for example, can be recovered nearly undecomposed, whereas the parent structure is totally decomposed.⁵¹

B. QUANTUM CHEMICAL RESULTS

The class of pseudoazulenes has attracted theoretical interest due to the analogy with hydrocarbon azulene.^{46,57,61,65,67,74,79–82,101,102,118,129,158,161,189} These calculations should also answer the question of whether the pseudoazulenes should be considered as heteroaromatic compounds. A large amount of work deals with the electronic spectra of the pseudoazulenes (see Section IV,E).^{54,57,60,62–64,67,74,96,117,118,170,191} Furthermore, there are calculations that are dedicated exclusively to questions of reactivity.^{61,126,133} These results, a portion of which have already been summarized,^{2,38} allow the following general remarks.

Pseudoazulenes possess a heteroaromaticity produced essentially by the $[4n + 2\pi]$ electron system extending over the ring periphery. The transannular bond between the five- and six-membered ring enforces coplanarity; thus, the pseudoazulenes can also be considered as bicyclic analogs of the heteronins.² Dipolar structures (Eq. 7) contribute to the resonance stabili-



zation. Similar relationships with azulene exist.¹²⁸

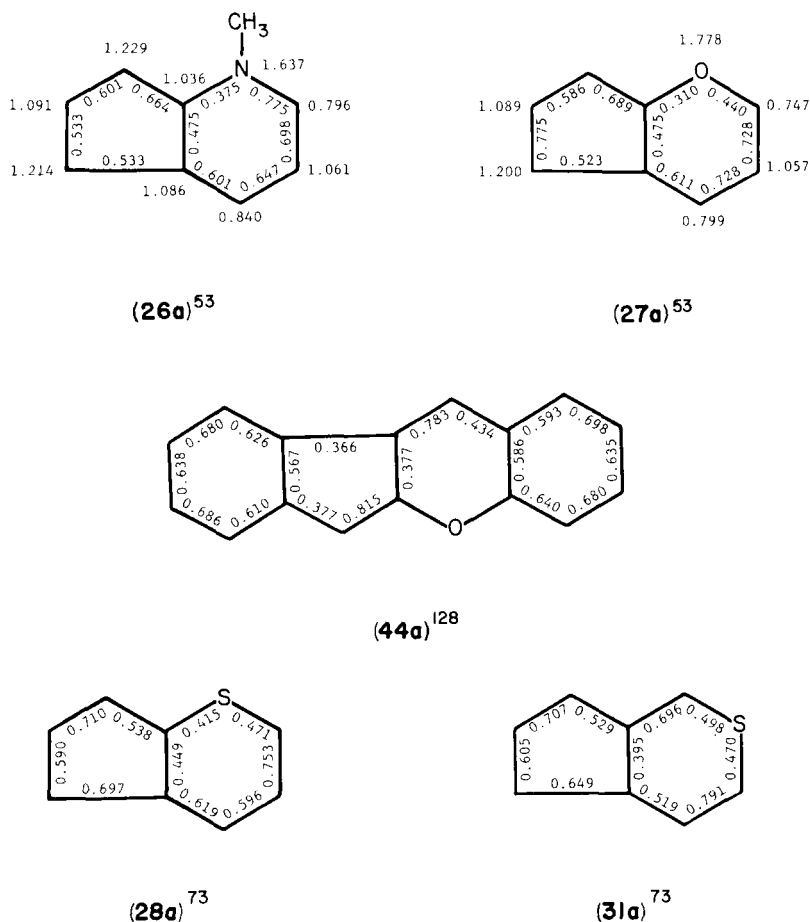
The calculated energies of delocalization (DE) and the bond lengths are dependent upon the heteroatom of the pseudoazulene. Using the HMO method, Borsdorf calculated the following DE values: for 1-methyl-1H-pyridine (**26a**), 2.79β ⁵⁷; for cyclopenta[*b*]pyran (**27a**), 2.66β ⁷⁴; for 2-phenylindeno[2,1-*b*]pyran (**33b**), 6.74β ²¹⁷; and for indeno[2,1-*b*]-1-benzopyran (**44a**), 6.29β .¹⁰² These values are confirmed by the resonance energies obtained by means of combustion and sublimation enthalpies.^{99,101} The calculated DE values for **26a** and **27a** are comparable to the resonance energy value of approximately 190 kJ/mol obtained for azulene.²¹⁸ These values show that the aromaticity of azalenes is higher than that of oxalenes. Similar results were also obtained by Boyd who calculated a decreasing order of aromaticity by the HMO method: **26**–**28** > **29**–**31** > **49**–**50** > **53**.^{71,134}

The aromaticity obtained by means of the DE values and their differences in the single pseudoazulene systems are also the result of calculations of the bond orders (Fig. 1). The calculated bond alternations^{46,57,77,79–82,117,118,129} are in line with the heteroaromaticity of the systems. Similar relationships were calculated for azulene.²¹⁹ The extent of the bond alternation, however, differs from one system to the other (see Fig. 1). In indeno[2,1-*b*]-1-benzopyran (**44a**) the bond lengths of the central cyclo[*b*]pyran system indicate pronounced bond alternation, and in the opinion of the authors, the systems have little aromatic character.¹²⁹ Calculations with 1H-pyridines (**26**) and 2H-pyridines (**29**) show that **26** is more stable than **29**, but both are less aromatic than indole.⁶³ A comparison of SCF calculations for pseudoazulenes **26** and **29** with their aza analogs **68** and **69**–**73**, which contain a pyrrole-type nitrogen, shows only minor perturbations of carbon–carbon bond lengths on replacing a $=\text{CH}-$ moiety by $=\text{N}-$.⁶⁶

²¹⁷ R. Borsdorf, unpublished results, in Schroth and Fischer.⁹⁹

²¹⁸ M. Gordon, *Chem. Rev.* **50**, 127 (1952); W. Treibs, W. Kirchhof, and W. Ziegenbein, *Fortschr. Chem. Forsch.* **3**, 334 (1955).

²¹⁹ H. K. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

FIG. 1. Quantum chemical results of bond orders (p_n) and electron densities.

Calculations of the Julg indices²²⁰ for oxalenes **40** and **44** (primarily for a study of electronic spectra)¹¹⁷ show also that these pseudoazulenes possess heteroaromaticity.

For all pseudoazulenes an electron deficiency in the six-membered ring and an excess in electrons in the five-membered ring were calculated (Fig. 1 and Eq. 7), again in accordance with azulene.²¹⁹ The heteroatom predominantly influences the electron density at the carbon atoms. As follows from calculations with identical parameter notations, the electronegativity of the heteroatom is essentially responsible⁵⁷ (see Fig. 1). In pseudoazulenes of

²²⁰ A. Julg, *Jerusalem Symp. Quantum. Chem. Biochem.* **3**, 383 (1971).

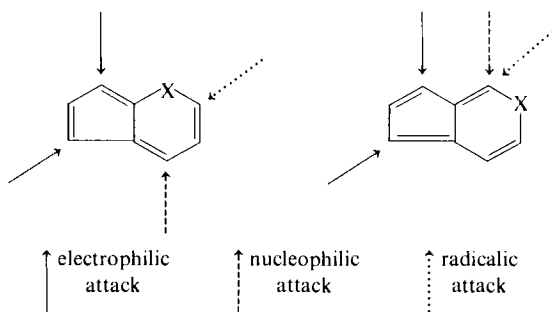
the $[b]$ -series the carbons of the five-membered ring have a higher electron density than those of the $[c]$ -series.⁷⁷ Condensation of benzene rings in the 5,6-position of 1*H*-pyrindines (**26** → **32**), cyclopenta[*b*]pyranes (**27** → **33**), and cyclopenta[*b*]thiopyranes (**28** → **34**) increases the electron density in the five-membered ring, whereas the electron density is decreased by condensation in the 2,3-position (e.g., **26** → **39**).⁵⁷ Electron densities at the single carbon of the five-membered rings are different: the carbon atoms that are directly bonded to the six-membered ring containing the heteroatom have a significantly higher density than the other carbons. By means of HMO calculations the following rules can be stated for simple systems.

1. If the heteroatom is in the 1-position ($[b]$ -series pseudoazulenes), the 5-position has a high electron density.
2. If the heteroatom is in the 2-position ($[c]$ -series pseudoazulenes), the 7-position has a high density.
3. The presence of a π -equivalent nitrogen atom (pseudoazulenes having one pyridine-type nitrogen) in the six-membered ring does not change the predictions in 1 and 2.⁶¹

The different electron density distribution causes a considerable dipole moment in the ground state of pseudoazulenes (Section IV.D). Corresponding calculations have been carried out for various systems.^{54,60,62,63,117,170,171}

Quantum chemical calculations also allow statements to be made about the reactivity of pseudoazulenes. The results have been generalized for simple systems in Scheme 15.

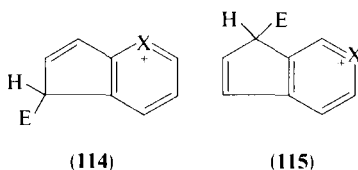
By means of two extreme models, i.e., the π -electron densities (q_r) of the ring atoms^{57,61,74,80,102,133} and the localization energy (L_r^+),^{61,126,133,221}



SCHEME 15

²²¹ R. D. Brown, *Q. Rev., Chem. Soc.* **6**, 63 (1952).

predictions about electrophilic reactions can be made. Commonly, the localization energy and the electron density calculations give opposite predictions of the preferred position of electrophilic substitution. The comparison with experimental results (see Section V.C) shows that the results based on L_r^+ parallel all known experiments, suggesting that the transition state for this reaction resembles the cationic intermediates (e.g., **114** and **115**).



Thus an electrophilic substitution takes place at C-5 and/or C-7. If both positions are unsubstituted, disubstitution can take place. Generally one can expect that in pseudoazulenes of the $[b]$ -series the 5-position is more reactive, whereas in the $[c]$ -series the 7-position is preferred.

Pseudoazulenes undergo nucleophilic and radical reactions. Compounds of the $[b]$ -series are attacked by nucleophiles at C-4 and those of the $[c]$ -series at C-1. The centers of radical reactions also change according to the position of the heteroatom: the $[b]$ -product reacts in 2-position and the $[c]$ -product in 1-position.

Comprehensive material concerning the calculation of electronic spectra of pseudoazulenes deals with the question of whether these compounds also possess the interesting absorption properties of the azulenes. The calculations show that all unsubstituted pseudoazulenes should possess a long-wavelength electronic transition between 500 and 700 nm, corresponding to an $S_0 \rightarrow S_1$ transition with π, π^* character. For simple representatives of the $[b]$ -series this long-wavelength transition is bathochromically shifted in the order of oxalenes to azulenes to thialenes.

Products of the $[c]$ -series should absorb hypsochromically as compared to those of the $[b]$ -series.^{63,64,66,79} Pseudoazaazulenes containing pyridine-type or pyrrole-type nitrogen absorb at shorter wavelengths than the corresponding compounds without nitrogen.^{62,170,171} According to the calculations, substituents should strongly influence the long-wavelength transition,^{57,118} as with azulenes.²²²

²²² Pl. A. Plattner, A. Fürst, and W. Keller, *Helv. Chim. Acta* **32**, 2464 (1949); E. Kloster-Jensen, E. Kovats, A. Eschenmoser, and E. Heilbronner, *ibid.* **39**, 1051 (1956).

²²³ H. L. Ammon and M. Sundaralingam, *J. Am. Chem. Soc.* **88**, 4794 (1966).

The transannular distances in azaazalenenes **56c** (pyridine-type nitrogen) are essentially shorter than those in other azulene-like compounds (between 1.47 and 1.52 Å).^{223a} This difference suggests that the canonical form contributes to the ground state resonance hybrid (Eq. 7). These experimental results are consistent with the quantum chemical calculations (see Section IV,B).

D. DIPOLE MOMENTS

The dipole moments of some pseudoazulenes were determined by dielectric measurements. They are listed in Table II. The high values obtained (for comparison: 6,6-dihydroindeno[2,1-*b*]quinoline has a dipole moment of 1.66 D whereas the corresponding 6-oxo compound has a value of approximately 1.6 D) are in accordance with quantum chemical calculations (see Section IV,B). The relatively high values of the dipole moments of unsubstituted pseudoazulenes and their derivatives show that some of the polar structures contribute to the resonance hybrid (Eq. 7). But in all cases the ring heteroatoms are localized at the positive end of the dipole.

Changes in the electric dipole moments of oxalenes **27**, **40**, and **44** between the ground and excited state have also been calculated.^{117,118}

TABLE II
DIPOLE MOMENTS OF SOME PSEUDOAZULENES

Compound	D (Debye units)	References
5-Methyl-5 <i>H</i> -indeno[2,1- <i>b</i>]quinoline	2.35	96
Indeno[2,1- <i>b</i>]-1-benzopyran	2.02	96
6-Carboethoxyindeno[2,1- <i>b</i>]-1-benzopyran	3.85	96
6-Formylindeno[2,1- <i>b</i>]-1-benzopyran	5.80	96
6-Nitroindeno[2,1- <i>b</i>]-1-benzopyran	6.10	96
2-Methyl-2 <i>H</i> -cyclopenta[<i>d</i>]pyridazine	2.83	148
2-Phenyl-2 <i>H</i> -cyclopenta[<i>d</i>]pyridazine	2.88	148
2-Methyl-5,7-dichloro-2 <i>H</i> -cyclopenta[<i>d</i>]-pyridazine	3.80	148
2-Methyl-5,6,7-trichloro-2 <i>H</i> -cyclopenta[<i>d</i>]-pyridazine	5.02	148
2-Methyl-5,6-di-trifluoroacetylcyclopenta[<i>d</i>]-pyridazine	6.71	148

^{223a} J. M. Robertson, H. M. M. Shearer, G. A. Sinn, and D. G. Walson, *Acta Crystallogr.* **15**, 1 (1962); G. Bastian and J. L. Derrison, *Acta Chem. Scand.* **20**, 1319 (1966).

E. ELECTRONIC SPECTRA

1. Absorption Spectra

Information about absorption spectra of pseudoazulenes can be found in nearly every paper mentioned in Table I. In most cases the spectral data provide a comparison with the corresponding azulene. For unstable pseudoazulenes electronic spectra are also used to demonstrate the structure of the product of synthesis.^{53,83,104,113,116,123,184,188,192} Systematic investigations on absorption spectra of pseudoazulenes have been made.^{63,66,68,69,92,96,117,118}

All pseudoazulenes possess an electronic transition in the visible spectral region (Table III). As can be derived from the extinction coefficient, as well as from investigations on solvent dependence, this electronic transition is a $\pi\pi^*$ transition having a low negative solvatochromism that can be measured for some compounds.^{51,86,145,165} These spectral data correspond to the results of quantum chemical calculations (Section IV,B) and are analogous to those of azulenes.

The values in Table III show the dependence of the localization of π band on the type of pseudoazulene.¹¹⁷ Uncondensed thialenes absorb at markedly longer wavelengths than azulenes; for condensed compounds the relationships are inverted or the absorption maxima are almost equal. Products of the $[h]$ -series absorb at longer wavelengths than those of the $[c]$ -series; pseudoazulenes containing a pyrrole- or pyridine-type nitrogen absorb at shorter wavelengths than those without nitrogen.

Systematic investigation of the influence of substituents upon long-wavelength absorption are scarce.^{69,96,117,118,146} The existing material, however, allows the conclusion that the direction and extent of the absorption shift are approximately the same as those in azulenes. Electron-accepting substituents (nitro, acetyl, and trifluoroacetyl groups) on the five-membered ring cause a hypsochromic shift, in contrast to the unsubstituted compounds. This fact has been reported for cyclopenta $[h]$ pyranes (**28**),⁷⁸ cyclopenta $[c]$ -thiopyranes (**31**),⁸⁶ indeno $[2,1-h]$ pyranes (**33**),⁹⁶ indeno $[2,1-h]$ -1-benzopyranes (**44**),⁶⁹ and 2*H*-cyclopenta $[d]$ pyridazines (**56**).¹⁴⁶

Methyl, methoxy, or phenyl groups and halides introduced at position 1 or 3 in the five-membered ring cause the $S_0 \rightarrow S_1$ transition to shift toward longer wavelengths: for phenyl groups it is 22 nm in 4*H*-cyclopenta $[b]$ quinolines (**39**)¹¹⁰ and 42 nm in cyclopenta $[h]$ -1-benzopyranes (**40**)¹¹⁰ (azulene is 26 nm²²²); for the methoxy group it is 42 nm in **39** and **40**¹¹⁰ (azulene is 45 nm²²²); and for halides it is between 10 and 21 nm in 2*H*-cyclopenta $[d]$ -pyridazines (**56**).¹⁴⁶ Anderson¹⁴⁶ recognized the additivity of the long-wave length absorption shifts in **56** caused by substituent groups. Thus, this

TABLE III
POSITION OF THE $S_0 \rightarrow S_1$ TRANSITION (nm) FOR
SOME SIMPLE PSEUDOAZULENES AND RELATED AZULENES

Compound	λ_{\max}	References
Azulene ^a	541, 558, 579, 603, 632 662, 697	222
1-Methyl-1 <i>H</i> -pyrindine ^a	442, 458, 468, 484, 502 520, 539, 568	56
2-Phenyl-2 <i>H</i> -pyrindine ^b	432	85
Cyclopenta[<i>b</i>]thiopyran ^a	537, 557, 580, 602, 634 661, 702	78
Cyclopenta[<i>c</i>]thiopyran ^b	465, 483, 500, 520, 542 565	85
7-Methyl-7 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine ^a	404, 415, 427, 440, 459	58
2-Methyl-2 <i>H</i> -cyclopenta[<i>d</i>]pyridazine	400	145
1,2-Benzazulene ^a	565, 615, 682, 742, 776	222
1-Methyl-1 <i>H</i> -indeno[2,1- <i>b</i>]pyridine ^a	490, 519, 542, 558, 591 611	92
2-Ethylindeno[2,1- <i>b</i>]pyran ^a	492	99
Indeno[2,1- <i>b</i>]thiopyran ^a	530, 555, 605, 621, 663 686	78
2-Methyl-2 <i>H</i> -indeno[2,1- <i>c</i>]pyridine ^c	620	94
1-Methyl-1 <i>H</i> -indeno[1,2- <i>b</i>]pyridine ^a	565, 604, 662, 711, 738 786	92
1,3-Diphenyl-2-methyl-1,2 <i>H</i> -indeno- [2,1- <i>c</i>]pyrazole ^b	490	135
1-Methyl-1 <i>H</i> -pyrido[2,3- <i>b</i>]indole ^c	319	173
2,4-Dimethylthiopyrano[2,3- <i>b</i>]indole ^b	435, 455	175
5,6-Benzazulene ^c	552, 531, 668	222
4-Methyl-4 <i>H</i> -cyclopenta[<i>b</i>]quinoline ^d	525, 555	113
2-Phenylcyclopenta[<i>b</i>]-1-benzopyran ^c	470	110
Cyclopenta[<i>b</i>]-1-benzothiopyran ^a	528	122
5-Methyl-5 <i>H</i> -cyclopenta[<i>c</i>]quinoline ^a	430	123
5-Methyl-5 <i>H</i> -indeno[2,1- <i>b</i>]quinoline ^c	531	110
Indeno[2,1- <i>b</i>]-1-benzopyran ^c	465	110
Indeno[2,1- <i>b</i>]-1-benzothiopyran ^c	500	110
5-Methyl-5 <i>H</i> -indeno[1,2- <i>b</i>]quin- oxaline ^c	579	110
Benzo[<i>b</i>]indeno[1,2- <i>e</i>]1,4-thiazine ^c	519	110
5-Methyl-5 <i>H</i> -indolo[2,3- <i>b</i>]quin- oxaline ^c	417	201

^a In cyclohexane.^b In *n*-hexane.^c In ethanol.^d In ether.

pseudoazulene retains the azulenic property of the additive effect of the substituents.²²⁴

The vibrational structure of the S_1 state of some oxalenes can be determined by means of Spolskij spectra^{68,69,117}. The long-wavelength absorption of pseudoazulenes as well as the influence of substituents can be explained by the following model supported by quantum chemical calculations^{117,118}: the dipole of the ground state (Section IV,D) is oriented from the six- to the five-membered ring (see Eq. 7) but in the excited state this orientation is changed. Therefore, the valence electrons are easily polarized, and only low energies are required for their transfer to the LUMO.

All pseudoazulenes absorbing at long wavelengths (500 nm) show a pronounced energy gap at S_1 – S_2 having values of approximately 120 kJ/mol.^{51,68,69,117} Thus, relationships are analogous to those of azulenes.²²⁵ This also expressed by the relatively long lifetime of the S_2 state. For 6-phenyl-indeno[2,1-*b*]-1-benzopyrane (**44b**) it amounts to 120 ps, as determined by ultrafast spectroscopy.

2. Emission Spectra

Some pseudoazulene systems show weak fluorescence (measured for **26**, **27**, **33**, **39**, **40**, **44**, **56**, and **68**).^{51,68,69,117,168,169,226} With the exception of pseudoazulenes **68**^{168,169} and **56**,¹²⁰ the emission by the other systems is due to the transition $S_2 \rightarrow S_0$. Thus, with respect to fluorescence spectra, many pseudoazulenes show essentially the same properties as azulenes.²²⁷ The quantum yields of fluorescence are very low (between 10^{-2} and 10^{-4}). They are markedly dependent upon the energy gap (S_1 – S_2) and the flexibility of the pseudoazulene systems. The fluorescence quantum yields increase when additional benzene rings are introduced onto the uncondensed ring skeletons of the pseudoazulene systems. A slight increase in quantum yields is also observed if halides or phenyl groups are introduced. To explain this anomalous fluorescence the energy-gap model²²⁸ and a quantum chemical model²²⁹ have been invoked; however, neither could explain all effects.^{69,117} Hitherto, no other luminescence spectra (particularly $S_1 \rightarrow S_0$ fluorescence and phosphorescence) have been observed for pseudoazulenes

²²⁴ A. G. Anderson, Jr., R. G. Anderson, and T. S. Fujita, *J. Org. Chem.* **27**, 4535 (1962).

²²⁵ G. Binsch, E. Heilbronner, R. Jankow, and D. Schmidt, *Chem. Phys. Lett.* **1**, 135 (1967).

²²⁶ P. Seybold, Ph.D. Thesis, Harvard University, Cambridge, Massachusetts (1967), cited in Anderson *et al.*¹⁴⁴

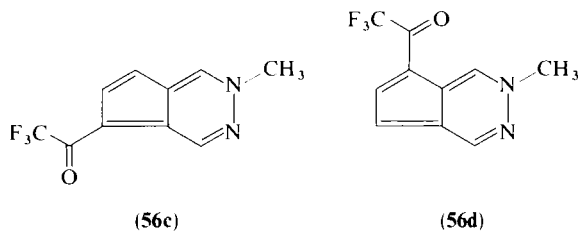
²²⁷ M. Beer and H. C. Longuet-Higgins, *J. Chem. Phys.* **23**, 1390 (1955).

²²⁸ S. Murata, C. Iwanaga, T. Toda, and H. Kokubun, *Ber. Bunsenges. Phys. Chem.* **76**, 1176 (1972).

²²⁹ F. Fratev, W. Monev, O. E. Polansky, S. Stojanov, and N. Tyutyulkov, *Z. Naturforsch. A* **32A**, 178 (1977).

showing anomalous fluorescence, although numerous measurements have been carried out on different pseudoazulene systems.²³⁰

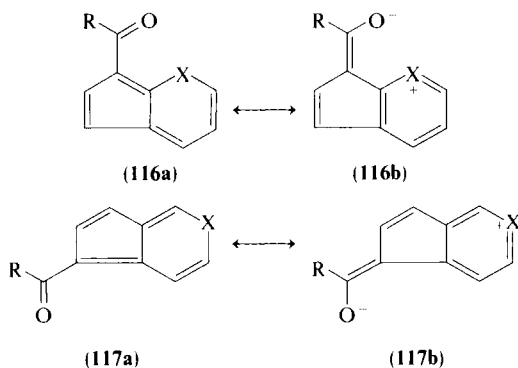
In the pseudoazulenes **56** and **68** the energy gap between S_1 and S_2 is small and therefore only normal $S_1 \rightarrow S_0$ fluorescence appears. The quantum yield of this fluorescence is higher than that of the $S_2 \rightarrow S_0$ fluorescence of



the other pseudoazulenes. The fluorescence quantum yields for **56c** and **56d** differ by a factor of 10.²²⁶ Both compounds show a phosphorescence with comparable quantum yields.

F. INFRARED SPECTRA

Systematic investigations on infrared spectra of pseudoazulenes have not been published. Data can be found only in the experimental sections of papers. Investigations on 2-phenyl-2*H*-pyridine (**29b**),⁸⁵ cyclopenta[*c*]thiopyran (**31a**),⁸⁵ 4-methyl-4*H*-cyclopenta[*b*]quinoline (**39a**),^{113,114} 5-methyl-5*H*-cyclopenta[*c*]quinoline (**42a**),¹²³ and oxalenes **27**, **33**, **40**, **44**²³¹ show that the absorption frequencies fall into three main regions: 600–1250 cm^{-1} (in-plane and out-of-plane bonding vibrations of CH), 1300–1620 cm^{-1} (aromatic C—C bonds), and 2980–3120 cm^{-1} (C—H stretching vibrations).



²³⁰ A. Olszowski and H.-J. Timpe, unpublished results (1977–1980).

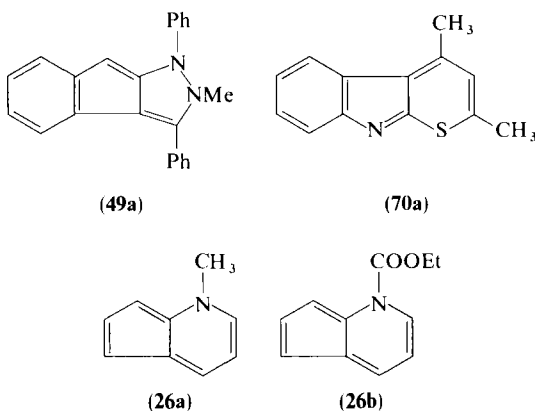
²³¹ A. Brunn and H.-J. Timpe, unpublished results (1980).

All these frequencies are in the region of other heteroaromatic compounds and of azulenes. Infrared absorption spectra for several derivatives of the following pseudoazulene systems have been reported: **26**,⁵⁶ **28**,⁷⁷ **29**,^{85,86} **33**,^{96,100} **35**,¹⁰⁵ **39**,^{113,114} **42**,¹²³ **49**,^{135,136} and **56**.^{143,144,146} The key frequencies for substituents at positions 1 or 3 in the five-membered ring are shifted to lower wavelengths in a typical manner. This is especially pronounced in the case of carbonyl groups.

The C=O absorption bands in trifluoroacetyl-substituted **56** have been determined to be between 1647 and 1653 cm^{-1} ,^{144,146} in benzoyl-substituted **49** at 1621 cm^{-1} ,¹³⁶ in formyl-substituted **49** at 1606 cm^{-1} ,¹³⁵ and in benzoyl-substituted **35** between 1625 and 1640 cm^{-1} .¹⁰⁰ Many authors have concluded that canonical forms **116b** and **117b** contribute greatly to the ground state resonance hybrid. Analogous frequency shifts have been found in the nitriles of indeno[2,1-*b*] series **34** and **33**.⁹⁶

G. NUCLEAR MAGNETIC RESONANCE SPECTRA

Chemical shift data for a number of simple pseudoazulenes are listed in Table IV. The signals for the protons of the pseudoazulenic skeleton are in the region of other heteroaromatic compounds. Also the NMR spectrum of **49a** shows a peak for the pseudoazulene ring protons at $\tau = 4.26$ ppm ($\delta = 5.74$ ppm)¹³⁵ and that of **70a** at $\tau = 3.25$ ppm ($\delta = 6.75$ ppm).¹⁷⁵ Many authors argue against substantial aromatic character for these pseudoazulene



systems^{55,56,85,93,123,146,163} in view of such high field shifts. This conclusion is supported by measurements of the solvent shift parameter S^{232} for compounds **26a** and **26b**.^{55,56} These compounds possess essentially the same

²³² F. A. L. Anet and G. E. Schenck, *J. Am. Chem. Soc.* **93**, 556 (1971).

TABLE IV
CHEMICAL SHIFTS (τ , ppm) OF RING PROTONS OF SOME SIMPLE PSEUDOAZULENES^a

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	References
1-Methyl-1 <i>H</i> -pyrindine	--	2.06	3.40	2.32	3.64	2.80	3.94	56
1-Carbethoxy-7 <i>H</i> -pyrindine	-	1.80	3.50	2.25	3.20	2.75	3.47	55
2-Phenyl-2 <i>H</i> -pyrindine	1.83		3.18	2.65	3.26	2.85	3.41	85
Cyclopenta[<i>c</i>]thiapyran	1.65		3.15	2.02	3.15	2.58	3.15	85
1-Methyl-1 <i>H</i> -indeno[2,1- <i>b</i>]-pyridine	—	1.92	3.75	2.00		2.26–3.02		93
2-Methyl-2 <i>H</i> -cyclopenta[<i>d</i>]-pyridazine	1.33	—	—	1.72	3.33	2.62	3.15	144
2-Methyl-5-chloro-2 <i>H</i> -cyclopenta[<i>d</i>]pyridazine ^b	1.40	—	--	1.45	--	2.97	3.37	146
2-Methyl-7-chloro-2 <i>H</i> -cyclopenta[<i>d</i>]pyridazine ^b	1.22			1.08	3.26	2.76		146
7-Phenacyl-7 <i>H</i> -pyrrolo-[2,3- <i>b</i>]pyridine ^b		2.00	3.35	1.87	2.95	1.67		166
4-Phenyl-4 <i>H</i> -cyclopenta[<i>c</i>]-cinnoline ^c	3.04	2.55	3.60				--	163
6,9-Dimethylthiopyrano-[4,3- <i>b</i>]indole	1.34	—	2.23	1.81		—	—	189
4-Methyl-4 <i>H</i> -cyclopenta[<i>b</i>]-quinoline ^d	4.17	2.50	3.60	—	2.26	1.90	2.5–2.1	123 114
5-Methyl-5 <i>H</i> -cyclopenta[<i>c</i>]-quinoline	3.26	2.9–2.78	3.05–2.98	2.22	--	1.9–1.74	2.78–2.69	123

^a τ can be converted to the more current use of δ , where $\delta = 10 - \tau$. Solvents are either CCl₄ or CDCl₃ unless stated otherwise.

^b Acetone-d₆

^c CS₂

^d 9-H: 1.90 ppm.

strong diatropic proton shifts (**26a**: $S = 1.7$ and **26b**: $S = 1.3$). This means that pseudoazulene **26** is as strongly diatropic as naphthalene or azulene (both having $S = 1.8$). From the criterion of solvent shift the delocalization of the system's lone pair is insensitive to variations in the electronegativity of the heteroatom.

The charge alternation indicated by quantum chemical calculations (Section IV,B and Fig. 1) is supported by NMR spectra. Different screening of C—H due to different π -electron densities gives rise to the chemical shifts of the ring protons. This means that those positions of the five-membered ring that are directly bonded to the six-membered ring are more strongly screened. This observation is also in accordance with theoretical predictions.

Carbon-13 magnetic resonance studies have been made only on 1-carbethoxy-5-trifluoroacetyl-1*H*-pyrindine (**26d**).⁵⁶ The chemical shifts of the ring carbons are as follows: 137.5, 136.7, 134.1, 131.0, 130.0, 112.7, 107.8, and 105.0 ppm.

The use of NMR spectroscopy made possible the investigation of protonation (see Section V,B)^{71,86,145} and of hydrogen–deuterium exchange phenomena in pseudoazulenes and their salts (see Section V,D).^{71,86,126,145}

H. MASS SPECTROSCOPY

Detailed studies of the mass spectra of pseudoazulenes have not been reported; data are only described in the experimental sections of papers, usually without any discussion. More detailed data have been reported for pseudoazulene systems **35** and **36**,¹⁰⁵ **39**,^{113,114} **42**,¹²³ **65**,¹⁶³ **80**,¹⁹⁵ **81**,¹⁹⁷ **82**,¹⁹⁸ and **83**.¹⁹⁸ Mass ion data have been reported for **26**^{55,56} and **56**.¹⁴³

The mass spectra of benzofused pseudoazulenes **65** and **80–83** show the mass ion as the base peak, and intense peaks are observed that correspond to the doubly charged molecular ion. The authors¹⁹⁷ have attributed this fact to the aromaticity of these systems. This conclusion, however, cannot be drawn for all pseudoazulenes since the relative intensity of the mass ion for **26b** is only 5.5%,⁵⁵ for 4-methyl-4*H*-cyclopenta[*b*]quinoline 64%,¹¹⁴ for 5-methyl-5*H*-cyclopenta[*c*]quinoline 7.0%,¹²³ and for 2-phenacyl-9-benzoyl-2*H*-indeno[2,1-*b*]pyridine 18%.¹⁰⁵

I. MISCELLANEOUS METHODS

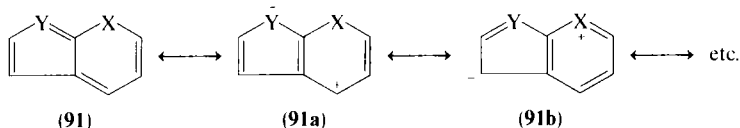
Polarographic data for pseudoazulenes **26**, **27**, **39**, and **40** have been reported.⁵¹ Reduction of azulenes **26** and **39** at a dropping mercury electrode using tetrabutylammonium perchlorate as the carrier electrolyte in acetonitrile

trile shows two half-wave potentials between -1.9 and -2.2 V. Under the same conditions oxalenes **27** and **40** show one reduction potential between -1.5 and -2.0 V. The combustion and sublimation energies of some 5*H*-indeno[2,1-*b*]quinolines (**43**) and indeno[2,1-*b*]-1-benzopyranes (**44**) have been reported.¹⁰¹

V. Chemical Properties

A. AROMATIC CHARACTER AND REACTIVITY

The classical structure of a pseudoazulene of the [*b*]-series (**91**) is inconsistent with its aromatic character and important dipole moments. A set of resonance structures involving dipolar forms such as **91a** and **91b** as contri-



butors seems to give a more accurate picture. The pseudoazulenes of the [*c*]-series show the same behavior. In pseudoazulenes containing a pyrrole-type nitrogen, dipolar forms having excess electrons at the nitrogen atom are expected to make an important contribution to the resonance hybrid. In fact, dipolar forms are also discussed for azulenes,²³³ but the contribution of ionic resonance structures in pseudoazulenes is more important than that in azulenes. Furthermore, one can expect that the importance of ionic resonance structures is strongly influenced by the identity of heteroatom X. This arises from the results of quantum chemical calculations (see Section IV,B); there are scarcely any systematic experimental measurements. As can be derived from the dipolar form **91b** pseudoazulenes can also have properties of enamines (e.g., for azalenes), enol ethers (e.g., for oxalenes), and thioenol ethers (e.g., for thialenes). The classical structure (**91**) shows that pseudoazulenes also formally contain structural elements of fulvenes.

For these reasons the reactivity of pseudoazulenes is higher than that of the carbocyclic analogs, the azulenes. Thus, a generally lower stability toward electrophilic, nucleophilic, and radical reagents results. This explains why the general stability of some pseudoazulenes is so low (see Section IV,A).

A special subject of comprehensive investigation is electrophilic attack (see Section V,C). This reaction can be considered to be an electrophilic aromatic substitution and also to be an electrophilic reaction with enamines,²³⁴ enol

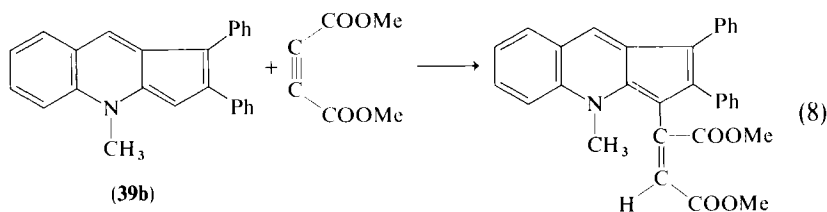
²³³ D. M. G. Lloyd, "Carbocyclic Non-benzenoid Aromatic Compounds," p. 291. Am. Elsevier, New York, 1966.

²³⁴ G. Laban and R. Mayer, *Z. Chem.* **8**, 165 (1968).

ethers,²³⁵ or thioenol ethers.²³⁶ Molecular orbital calculations (see Section IV,B) predict that electrophilic attack should preferentially occur at those carbon atoms of the five-membered ring that are directly bonded to the six-membered ring. Investigations, however, have been almost always restricted to qualitative observations; quantitative results have been reported only recently.^{147,149}

Considerably fewer examples have been reported for the nucleophilic attack on the pseudoazulene ring or for the nucleophilic substitution of substituents in the pseudoazulene ring. Apparently there is no example of a reaction of a free radical with a pseudoazulene.

Reactions in which pseudoazulenes formally react as dienes are unknown. Experiments with the Diels–Alder reaction of pseudoazulenes **26**, **27**, **39**, and **40** have not been successful. With dimethyl acetylene dicarboxylate in cold benzene or methylene chloride these pseudoazulenes react by addition (Eq. 8).²³⁶



Systematic investigations of oxidation and reduction reactions of pseudoazulenes are not available. Many pseudoazulenes are sensitive to air but their reaction behavior with other oxidizing reagents is unknown. The air sensitivity of many pseudoazulenes is inconsistent with the aromaticity of these compounds.

Very different results are obtained by hydrogenation of pseudoazulenes. Chemical and catalytic reduction gives a variety of products. The six-membered ring, however, is often perhydrogenated; these reactions are discussed in Section V,E.

B. PROTONATION

Protonation represents the simplest electrophilic reaction. Contrary to azulene ($pK_a = -1.7$)²³⁷ most pseudoazulene systems are relatively strong bases. The pK_a values are listed in Table V. Numerous pseudoazulenes can be obtained from their quaternary salts by the action of sodium acetate (see

²³⁵ F. Effenberger, *Angew. Chem.* **81**, 374 (1969).

²³⁶ H.-J. Timpe and A. Al-Shoraji, *Z. Chem.* **21**, 448 (1981).

²³⁷ F. A. Long and J. Schulze, *J. Am. Chem. Soc.* **86**, 327 (1964).

TABLE V
p*K_a* VALUES OF SOME PSEUDOAZULENES

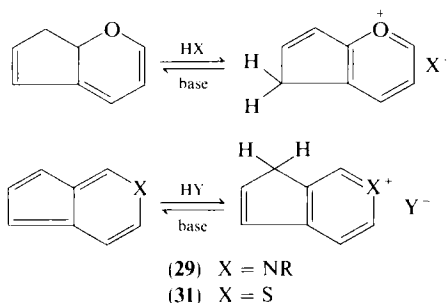
Compound	p <i>K_a</i>	References
1-Methyl-1 <i>H</i> -indeno[2,1- <i>b</i>]pyridine ^a	12.5	92
2-Methyl-2 <i>H</i> -cyclopenta[<i>d</i>]pyridazine ^b	1.95	145
7-Methyl-7 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine ^b	8.55, 5.2	166, 167
7-Phenacyl-7 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine ^b	7.85	166
1-Methyl-1 <i>H</i> -pyrido[2,3- <i>b</i>]indole ^a	7.75, 7.55	35, 176
1-Methyl-1 <i>H</i> -pyrido[3,2- <i>b</i>]indole ^a	10.77	176
2-Methyl-2 <i>H</i> -pyrido[3,4- <i>b</i>]indole ^a	11.10, 10.88	35, 176
2-Methyl-2 <i>H</i> -pyrido[4,3- <i>b</i>]indole ^a	10.54	35
2,4-Dimethylthiopyrano[2,3- <i>b</i>]indole ^b	5.10	175
2-Methyl-4-phenylthiopyrano[2,3- <i>b</i>]indole ^b	3.60	175

^a Measured in 60% ethanol at 20 °C potentiometrically, using the methiodides.

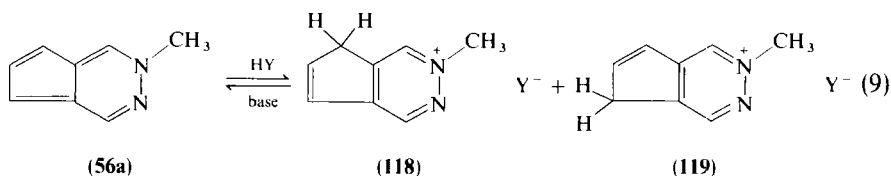
^b Measured in aqueous media at 25 °C spectrometrically.

Section III,A,1); they are considerably stronger bases than the acetate ion (p*K_a* > 4.5). The measured p*K_a* values, however, do not allow general statements to be made about the correlation between p*K_a* and molecular structure. Cyclopenta[*c*]thiopyran (**31a**) is a weaker base than 2-phenyl-2*H*-pyridine (**29b**),⁸⁶ but 2-methyl-2*H*-cyclopenta[*d*]pyridazine (**56a**) is even weaker than **31a** and **29b**.¹⁴⁵ This can probably be attributed to the inductive effect of the additional π -equivalent nitrogen in **56b** (see basicity of pyridazine and pyridine). Thus, the weaker basicities of pseudoazulenes containing pyrrole-type nitrogen atoms as compared to the analogous skeletons without this nitrogen can also be explained by the inductive effect of the heteroatom. For the pyrido-indole series it was found that pseudoazulenes having a quinoid structure as an important contributor are stronger bases.^{35, 176}

Because of the high electron densities at these positions protonation of unsubstituted pseudoazulenes should take place at a 1- and/or 3-position of the five-membered ring. As was investigated in more detail for the cyclopenta[*b*]pyran series (e.g., **27** and **40**) by NMR protonation takes place



exclusively at 5-position.⁷¹ HMO calculations on the nitrogen and sulfur analogs reveal the same position of protonation for these systems (see Section IV,B). Pseudoazulenes of the [c]-series were protonated only at the 7-position as seen by NMR spectra.⁸⁶ This site of protonation in both series is consistent with that in azulene (position 1).^{86,238} The protonation at nitrogen of pseudoazulenes containing a pyrrole-type nitrogen fits this pattern.^{35,166,175,176} Protonation at both 5- and 7-positions takes place in pseudoazulene **56** (Eq. 9). In the conjugated acid of 2-methyl-2*H*-cyclopenta-[*d*]pyridazine (**56a**) the ratio of the two species was determined by NMR spectroscopy to be 2.7:1 (**118**:**119**).¹⁴⁵ Also in 1,2*H*-indeno[2,1-*c*]pyrazoles



(**49**) the protonation takes place at the expected position of the cyclopentadiene ring as demonstrated by the disappearance of the vinyl proton signals in the spectra of the bases (**49**) when dissolved in trifluoroacetic acid and by the appearance of a two-proton methylene singlet near $\tau = 6$ ppm ($\delta = 4$ ppm).¹³⁵

Interestingly in these cases protonation takes place at the ring carbon, whereas for 5-azaazulene protonation occurs at the π -equivalent nitrogen, thus retaining the aromatic π -electron structure.²³⁹

Several authors have reported that they did not succeed in isolating a number of pseudoazulenes when solutions in dilute mineral or glacial acetic acids were diluted with water or other bases.^{51,71,77,86} It was only possible to recover polymer-like material. In the subsequent decomposition the nucleophile attacks the conjugated acid of the pseudoazulenes at a position adjacent to the heteroatom, probably resulting in a fission. The hydrogen-deuterium exchange catalyzed by acids has been reported for systems **29**,⁸⁶ **31**,⁸⁶ and **49**.¹³⁵

C. ELECTROPHILIC SUBSTITUTION REACTIONS

A considerable number of electrophilic substitution reactions are known for pseudoazulenes. They are listed in Table VI. Electrophilic substitution reactions of pseudoazulenes take place at C-1 and C-3 of the five-membered

²³⁸ S. S. Danyluk and W. G. Schneider, *J. Am. Chem. Soc.*, **82**, 998 (1960).

²³⁹ K. Hafner and M. Kreuder, *Angew Chem.*, **73**, 657 (1961).

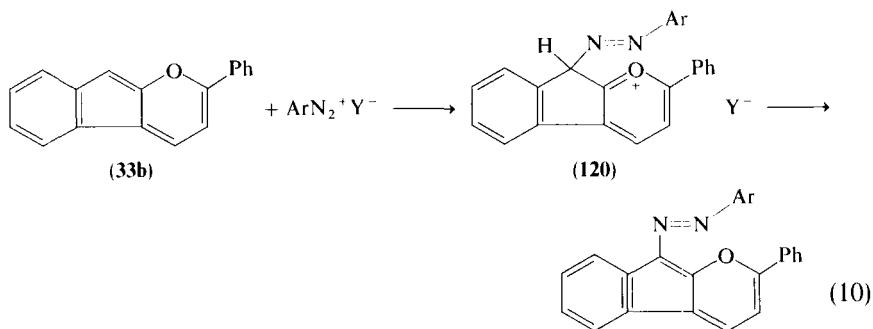
TABLE VI
 ELECTROPHILIC SUBSTITUTIONS ON PSEUDOAZULENE SYSTEMS

Type of Reaction	Pseudoazulene system
Chlorination ^a	27, ⁷² 28, ^{77,78,77b} 31, ^{86,88} 34, ⁷⁸ 41, ¹²² 56, ^{146,149}
Bromination ^c	27, ⁷² 31, ^{86,88} 40, ¹¹⁸ 44, ¹²⁷ 56, ^{57,138,146} 57, ¹³⁸ 65, ¹⁶⁴ 68, ¹⁶⁹
Iodination ^d	56, ¹⁴⁶
Nitration ^e	27, ^{72f} 28, ^{77,78} 31, ^{86,88} 44, ¹²⁷ 65, ¹⁶⁴
Mercuration	31, ⁸⁶ 40, ¹²⁰
Vilsmeier-Haak Reaction	27, ⁷² 33, ¹⁰⁰ 40, ^{118,120} 43, ¹²⁵ 44, ¹²⁷ 56, ¹³⁸ 57, ¹³⁸
Acylation	26, ⁵⁶ 28, ^{77,78} 31, ^{86,88} 39, ^{109,115} 42, ¹¹⁵ 43, ¹¹⁵ 44, ^{127,128} 45, ¹³¹ 49, ^{135,136} 56, ¹⁴⁴ 65, ¹⁶⁴
Alkylation	27, ⁷² 39, ¹¹⁴ 40, ¹¹⁹ 49, ¹³⁵ 66, ^{20,179} 68, ^{166,167} 71, ¹⁷⁶ 72, ^{13,17,21} 73, ¹⁸ 76 ³⁰
Azocoupling	26, ⁵¹ 27, ^{51,72} 31, ⁸⁶ 39, ⁵¹ 44, ¹²⁷ 49, ¹³⁵ 56, ¹⁴⁷ 65, ¹⁶⁴ 68 ¹⁶⁶
Enylation	27, ⁷² 33, ^{97,100} 44, ^{127,128} 49 ¹³⁵
Thiocyanation	31 ^{86,88}

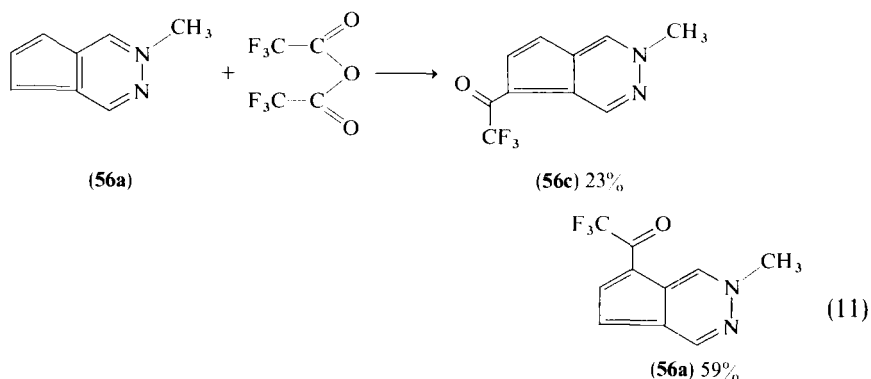
^a With *N*-chlorosuccinimide.^b With chloroanile.^c With *N*-bromosuccinimide.^d With *N*-iodosuccinimide.^e With tetranitromethane.^f With cupric nitrate in acetic anhydride.

ring having high π -electron densities (see Section IV,B and Section IV,G). Thus, electrophilic attack is easily facilitated and even weak electrophiles are able to react. Examples include acylations; these reactions, which normally are possible for hydrocarbons only under the conditions of Friedel-Crafts acylation, are possible for pseudoazulenes even without any catalyst. Acylations with oxalyl chloride or bromide^{78,127} proceed especially easily.^{56,61,144} If Friedel-Crafts catalysts are used, the yields sometimes are low because the pseudoazulenes or their conjugated acids are apparently decomposed by the catalysts. Electrophilic substitution reactions cannot be performed in acidic media because protonation predominates (see Section V,B), and the resulting cations are not able to undergo an S_E reaction. Thus, cyclopenta[*c*]thiopyran (**31a**) cannot be nitrated by nitric acetic anhydride, whereas nitration by tetranitromethane is successful.⁸⁶

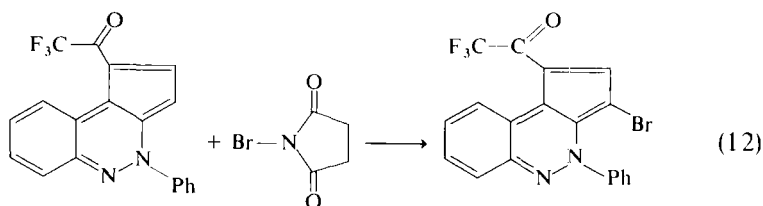
Another characteristic of electrophilic reactions of pseudoazulenes is the application of numerous cations as the electrophile, for example, diazonium salts and Vilsmeier-Haack's reagent (see Table VI), tropylium ion,¹³⁵ triphenylmethyl cation,¹¹⁴ pyrylium ion,¹¹⁹ and dithiolium ion.¹⁶⁶ Very stable cations are formed (e.g., **120**); addition of base releases the substituted pseudoazulene (see example in Eq. 10). Generally reactions of this type are thermodynamically favored (see also Section IV,B). The site of substitution



on the five-membered ring is easily detected by NMR spectroscopy (see Table IV). If both carbons are directly bonded to the six-membered ring containing the heteroatom, then both positions can be substituted. In the *[c]*-series the amount of 7-substitution product is greater than that of 5-substitution product,^{86,144,146} whereas in the *[b]*-series the 5-substitution product predominates.^{56,164} One such example is shown in Eq. 11.¹⁴⁴ This outcome is in agreement with quantum chemical calculations (see Section IV,B).



Excess electrophilic reagent leads to disubstitution at the five-membered ring in unsubstituted pseudoazulenes.^{51,115,144-147,164} Products of mono-substitution, even if they possess an acceptor substituent, can also be sub-



stituted once more with another electrophilic reagent (Eq. 12).¹⁶⁴ Once again the high nucleophilicity of the five-membered ring is shown. Efforts to obtain trisubstitution products from 5,7-dichloro-2-methyl-2*H*-cyclopenta-*[d]*pyridazine result only in polymer-like materials,¹⁴⁶ contrary to 1,3-dichloroazulene, which undergoes further electrophilic substitution.²⁴⁰

Competition experiments with pairs of reactants show that for electrophilic monochlorination with *N*-chlorosuccinimide, the relative reactivities of 2-methyl- and 2-phenyl-2*H*-cyclopenta-*[d]*pyridazine (**56a** and **56b**) were 5:1, respectively.¹⁴⁹

Only a few investigations of electrophilic substitution reactions of pseudoazulenes containing a pyrrole-type nitrogen have been reported. There are many examples of alkylations (see Table VI). An alkylation always takes place at the nitrogen of the five-membered ring. For 7*H*-pyrrolo[2,3-*b*]-pyridine **68** azocoupling and reaction with dithiolium salts have been reported.¹⁶⁶

D. REACTIONS WITH NUCLEOPHILES

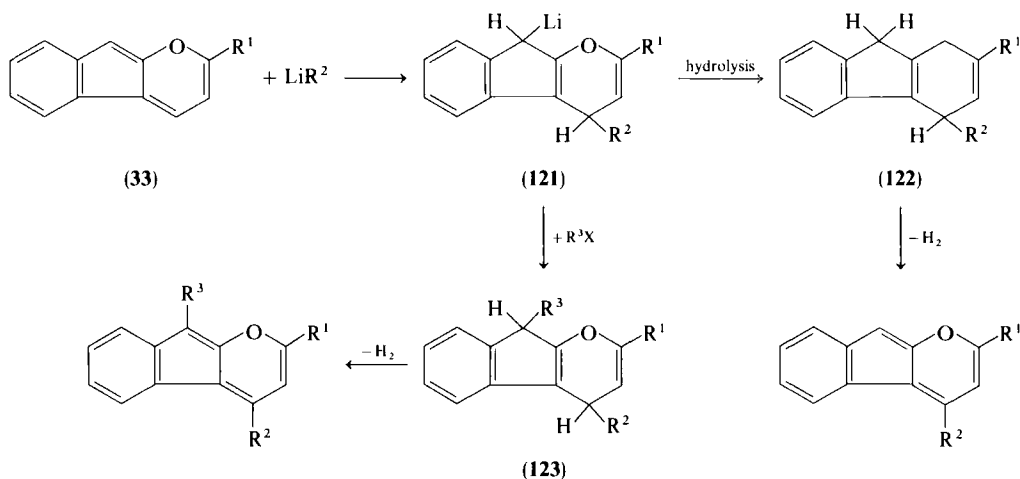
The treatment of cyclopenta-*[c]*thiapyrane (**31a**) with potassium *t*-butoxide in 95% O-deuterated *t*-butyl alcohol at room temperature resulted in more than 90% deuteration at the 1- and 3-positions and less than 5% at the 4-, 5-, 6-, and 7-positions.⁸⁶ Thus, the hydrogen-deuterium exchange takes place at the positions calculated by quantum chemistry (see Section IV,B). Completely analogous is the same reaction in the indeno[2,1-*b*]-1-benzopyrane system (**44**).¹²⁶

Lithium alkyls or aryls add to pseudoazulenes **33**^{98,100} and **39**.^{113,114} The carbanion always reacts with the carbon atom opposite the heteroatom in the six-membered ring (Scheme 16). After hydrolysis of primary intermediate **121** dihydro products (**122**) are formed, which can be transformed to pseudoazulenes in the usual manner (see Section III,A,2). The structure of primary intermediate **121** is confirmed by its alkylated (or acylated) products (**123**). Even these compounds can easily be dehydrogenated to pseudoazulene. In this way, substituted pseudoazulenes can be formed that are not obtainable otherwise. The direction of addition to the pseudoazulenes is the same as in azulenes.²⁴¹

Halide atoms at the five-membered ring of pseudoazulenes can be substituted by different nucleophiles. The reaction of 5,7-dichlorocyclopenta-*[c]*thiapyrane (**31b**) with silver nitrite in ethanol at reflux gave a chloronitro derivative (**31c**) in 46% yield.⁸⁶ Loss of halide from **31b** formed positive

²⁴⁰ A. G. Anderson, Jr. and L. L. Replogle, *J. Org. Chem.* **28**, 2578 (1963).

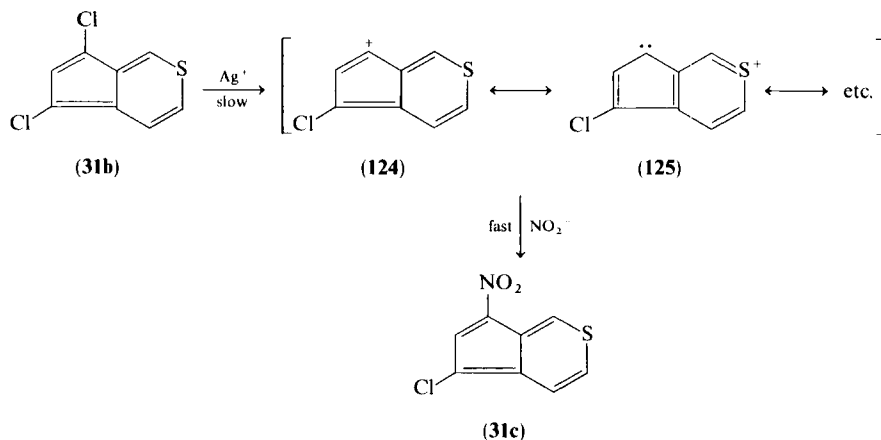
²⁴¹ K. Hafner and H. Weldes, *Justus Liebigs Ann. Chem.* **606**, 90 (1957).



SCHEME 16

species **124**, which was stabilized by delocalization of the positive charge (**125**) (Scheme 17) in the rate-determining step. Thus, relationships are analogous to those in correspondingly substituted azulenes.^{86,146,242}

The bromine atom of 11-bromobenzo[*b*]indeno[1,2-*e*]1,4-thiazine (**67a**) can be replaced by a cyanide, phenyl mercaptide, or hydroxyl group.²⁴³ Substitution should occur through the usual addition-elimination mechanism.



SCHEME 17

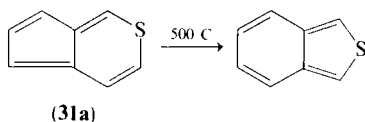
²⁴² K. Hafner, H. Patzeld, and H. Kaiser, *Justus Liebigs Ann. Chem.* **656**, 24 (1962).

²⁴³ F. G. Bordwell, T. W. Cutshall, and T. S. Rinderspecker, *J. Org. Chem.* **33**, 3308 (1968).

E. MISCELLANEOUS REACTIONS

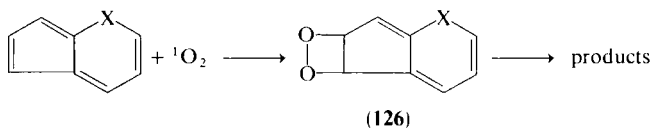
Hydrogenation has been predominantly used to elucidate the structures of alkaloids having pseudoazulene lattices. The different sites of addition, however, strongly decrease its use in structure proof. A single pseudoazulene can react under the same conditions at different positions. For example, although 7*H*-pyrrolo[2,3-*b*]pyridines (**68**) are hydrogenated by a Pt catalyst with simultaneous ring fission,¹⁶⁷ 2*H*-pyrido[3,4-*b*]indoles (**72**) hydrogenate either at the benzene³³ or at the heterocyclic ring.^{30,206} Hydrogenation of the heterocyclic six-membered ring is also possible with NaBH₄.^{32,178} However, 1*H*-pyrido[2,3-*b*]indoles (**69**) do not react with NaBH₄.³² 2*H*-Pyridines (**29**) (see Section III,A,2) can be perhydrogenated by an Rh catalyst.⁸⁵

Azulene can be thermally transformed to naphthalene. An analogous isomerization is known for cyclopenta[*c*]thiapyrane (**31a**).⁸⁵ If **31a** was kept



at approximately 500°C and at a pressure of 1 mm for 40 minutes, thianaphthalene was obtained in 9.5% yield. On the contrary, from the thermolysis products of cyclopenta[*b*]thiopyran (**28a**), an analogous isomerization product could not be isolated.⁷⁸

Closer investigations of pseudoazulenes **26**, **27**, **39**, and **40**^{50,214} revealed that irradiation of these systems in the presence of ³O₂ produced singlet oxygen. It was possible to demonstrate the formation of ¹O₂ by quenching experiments with DABCO and 2,5-dimethylfuran. In a thermal reaction ¹O₂ adds to the pseudoazulenes, whereby dioxetane derivatives (**126**) are



formed. These compounds cannot be isolated in a pure form since they decompose to several products already at room temperature. The decomposition of **126** takes place with luminescence.

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Chemistry of Pyrido[1,2-*a*]pyrimidines

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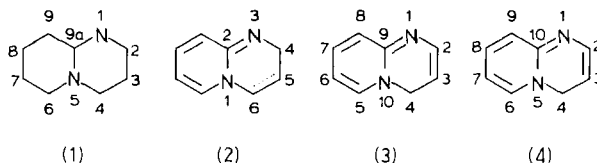
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I. Introduction

The chemistry of the pyrido[1,2-*a*]pyrimidines has previously been reviewed by Mosby¹, who found 43 references to this ring system while covering the literature up to 1957. Many of the early articles have been found to contain erroneous statements, and therefore these publications have also been included in the present work.

In the present review the primary chemical literature up to the end of 1981 has been surveyed. *Chemical Abstracts* Subject and Chemical Substance Indexes up to and including Volume 94 have been searched. Throughout this chapter the name and numbering style favored by *Chemical Abstracts* is used, i.e., pyrido[1,2-*a*]pyrimidine for ring system (1). Earlier names to designate the pyrido[1,2-*a*]pyrimidine derivatives include 1,2-divinylene-pyrimidine (for numbering cf. 2), 1,2-(dihydropyrido-1',2')-5,6-dihydropyrimidine, malonyl- α -aminopyridine, 4,10-dihydro-1,10-diazanaphthalene (3), 1,4*a*-diazanaphthalene, homopyrimidazole (4), 1-azadehydroquinolizinium, 1-azaquinolizium, 1-azaquinolizidine, 1,5-diazabicyclo[4,4,0]decane, and 1,5-diazabicyclo[4,4,0]dec-5-ene.



Certain types of pyrido[1,2-*a*]pyrimidines have aroused much interest owing to their valuable pharmacological properties. They are also used as synthetic intermediates or as additives to photographic materials and dyes. In the following sections the syntheses, reactions, physicochemical properties, and briefly the utilization of the pyrido[1,2-*a*]pyrimidines are discussed. Within the individual sections the pyrido[1,2-*a*]pyrimidinium salts, followed by the 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines, 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines, 2-oxo-3,4-dihydro-2*H*- and 4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines, and finally miscellaneous pyrido[1,2-*a*]pyrimidines are dealt with.

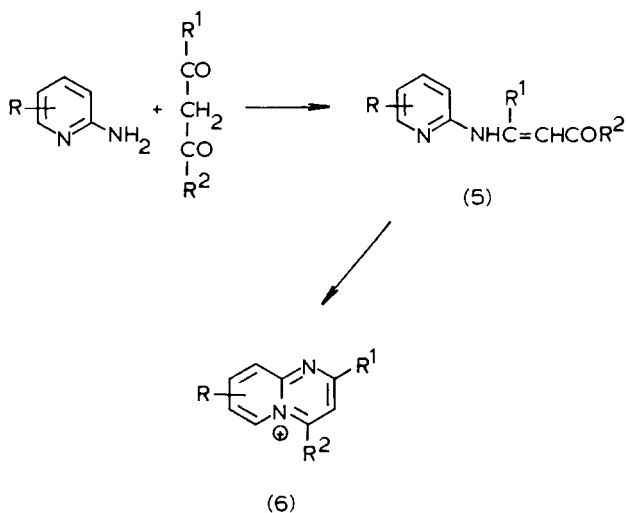
¹ W. L. Mosby, in "Heterocyclic Systems with Bridgehead Nitrogen Atoms," (A. Weissberger, ed.), Part II, p. 1141. Wiley-Interscience, New York, 1961.

II. Preparation of Pyrido[1,2-*a*]pyrimidines

A. PYRIDO[1,2-*a*]PYRIMIDINIUM SALTS

Pyrido[1,2-*a*]pyrimidinium salts (**6**), which are of aromatic character, are easily formed from 2-aminopyridines and 1,3-dioxo compounds²⁻⁵ or the acetal and ketal equivalents of the latter,⁴⁻¹⁰ in acidic media (perchloric acid and concentrated hydrobromic acid). The acidic conditions may also be provided by using the salts (hydroperchlorate and hydroiodide) of the 2-aminopyridines.^{2,4} When the reaction is conducted in the absence of acid, the intermediate enamine (**5**) can be isolated.^{5,6}

The reaction of β -oxo acetals and 2-aminopyridines unsubstituted in position 6 leads to 4-substituted pyrido[1,2-*a*] pyrimidinium salts (**6**; $R^1 = H$),^{5,7} whereas the 6-substituted 2-aminopyridines give rise to 2-substituted pyrido[1,2-*a*]pyrimidinium salts (**6**; $R^2 = H$).⁵



² K. T. Potts, R. Dugas, and C. R. Surapaneni, *J. Heterocycl. Chem.* **10**, 821 (1973).

³ V. A. Chuiguk and A. M. Khmaruk, *Ukr. Khim. Zh.* **41**, 186 (1975) [*CA* **83**, 9972 (1975)].

⁴ A. M. Khmaruk, Yu. M. Volovenko, and V. A. Chuiguk, *Ukr. Khim. Zh.* **38**, 262 (1972) [*CA* **76**, 153698 (1972)].

⁵ J. R. H. Sawyer and D. G. Wibberley, *J. C. S. Perkin I*, 1138 (1973).

⁶ A. N. Nesmeyanov, M. I. Rybinskaya, and N. K. Belskii, *Dokl. Akad. Nauk SSSR* **113**, 343 (1957) [*CA* **51**, 14712 (1957)].

⁷ A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR* **118**, 297 (1958) [*CA* **52**, 10080 (1958)].

⁸ A. Pollak, B. Stanovnik, and M. Tisler, *J. Org. Chem.* **36**, 2457 (1971).

⁹ S. Tamura and M. Ono, *Chem. Pharm. Bull.* **26**, 3167 (1978).

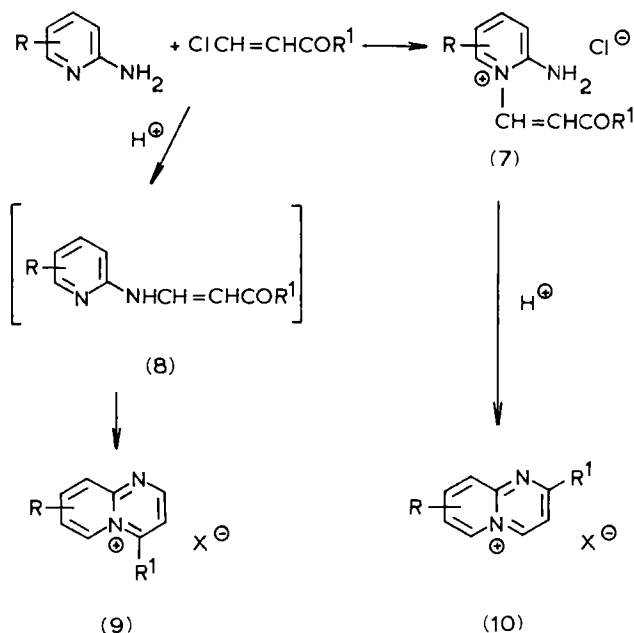
¹⁰ W. K. Franke, R. D. Henkler, and J. Küther, *Fette, Seifen, Anstrichm.* **82**, 370 (1980).

Reaction of 1,3-diketones and 2-aminopyridines led to 2,4-disubstituted pyrido[1,2-*a*]pyrimidinium salts (**6**: R^1 and $R^2 \neq H$), but the 6-substituted 2-aminopyridine failed to provide the bicyclic product.^{4,5} The irregular behavior of the 6-substituted 2-aminopyridines is explained by the steric hindrance effect of the 6-substituent.

Ring closure proceeded with 2,6-diaminopyridine, but instead of the 6-amino-2,4-disubstituted-pyrido[1,2-*a*]pyrimidinium salts, 2-amino-5,7-disubstituted-1,8-naphthyridines were formed.^{4,11}

Sawyer and Wibberley⁵ demonstrated that the product obtained by Singh *et al.*¹² in the reaction of 2-amino-4-methylpyridine and acetylacetone in polyphosphoric acid was not the naphthyridine but was instead the enamine of type **5**, which was formed by hydrolysis of the pyrido[1,2-*a*]pyrimidinium salt (**6**) when the reaction mixture was neutralized. Formation of both isomeric pyrido[1,2-*a*]pyrimidinium salts with asymmetric 1,3-diketones ($R^1 \neq R^2$) was occasionally observed.³

Pyrido[1,2-*a*]pyrimidinium salts were obtained as products when 1,2-diaminopyridinium iodide² was used instead of 2-aminopyridine, and triacylmethanes⁴ instead of 1,3-diketones. In the latter case ring closure was



¹¹ J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *J. Am. Chem. Soc.* **69**, 1151 (1947).

¹² S. Singh, R. S. Taneja, and K. S. Narang, *Indian J. Chem.* **6**, 11 (1968).

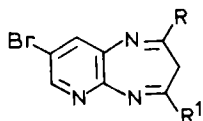
accompanied by deacylation. β -Chlorovinylaldehydes¹³ and β -chlorovinyl ketones^{3,7,14-16} have also been utilized as 1,3-bifunctional components.

According to Chuiguk and Oksanich¹³ the reaction of 2-aminopyridinium perchlorates and β -chlorovinylaldehydes led exclusively to the 4-substituted products (9) whereas from 2-amino-6-methylpyridine no cyclic product was obtained. With β -chlorovinyl ketones both the 2- and 4-substituted pyrido[1,2-*a*]pyrimidinium salts were detected by ¹H NMR.³ 2-Amino-6-methylpyridine gave rise only to the 2-substituted isomer (10).

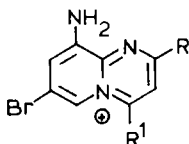
Reactions of 2-aminopyridines with β -chlorovinyl ketones were surveyed by Fischer.¹⁶ He established that in a nonacidic medium (acetone-methanol mixture) the pyridinium salts (7) are formed, which can then be cyclized by acids (acetic acid and 70% perchloric acid) to the 2-substituted pyrido[1,2-*a*]pyrimidinium salts (10).^{14,15} In acidic media, however, the 4-substituted pyrido[1,2-*a*]pyrimidinium salts (9) are formed via the enamine (8).^{6,16}

Fischer^{14,15} prepared the unsubstituted pyrido[1,2-*a*]pyrimidinium salt (16) and its 4-phenyl derivative (9: R¹ = Ph) by reacting 2-aminopyridinium perchlorate with propargylaldehyde and with ethynyl phenyl ketone, respectively.

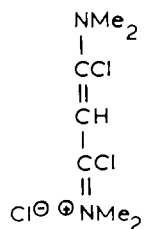
Reaction of 2,3-diamino-5-bromopyridinium perchlorate and acetylacetone⁴ or β -chlorovinylaldehyde¹³ did not provide the expected pyrido[2,3-*b*](1,4)diazepines (11), but provided instead the pyrido[1,2-*a*]pyrimidinium salts (12).



(11)



(12)



(13)

Antus-Ercsenyi and Bitter¹⁷ prepared the first representative of the 2,4-diaminopyrido[1,2-*a*]pyrimidinium salts by reacting 13 and 2-aminopyridine. In a freshly made solution of 14 in 0.5 *N* hydrochloric acid, Tamura and

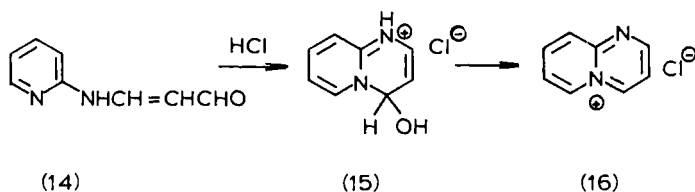
¹³ V. A. Chuiguk and V. V. Oksanich, *Khim. Geterotsikl. Soedin.*, 242 (1973) [*CA* 79, 6745 (1973)].

¹⁴ G. W. Fischer, *J. Prakt. Chem.* 316, 474 (1974).

¹⁵ G. W. Fischer, German (East) Patent 113,542 [*CA* 84, 105647 (1976)].

¹⁶ G. W. Fischer, *Z. Chem.* 18, 121 (1978) [*CA* 89, 23666 (1978)].

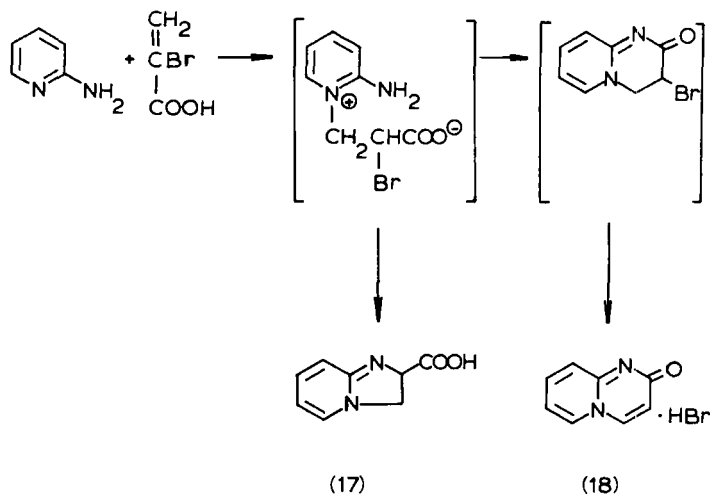
¹⁷ A. Antus-Ercsenyi and I. Bitter, *Acta Chim. Acad. Sci. Hung.* 99, 29 (1979) [*CA* 91, 175230 (1979)].



Ono⁹ detected the corresponding 4-hydroxy derivative (15) by ¹H NMR, in addition to the pyrido[1,2-*a*]pyrimidinium chloride (16). After 90 min, only the signals of 16 were found in the spectrum.

B. 2-Oxo-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

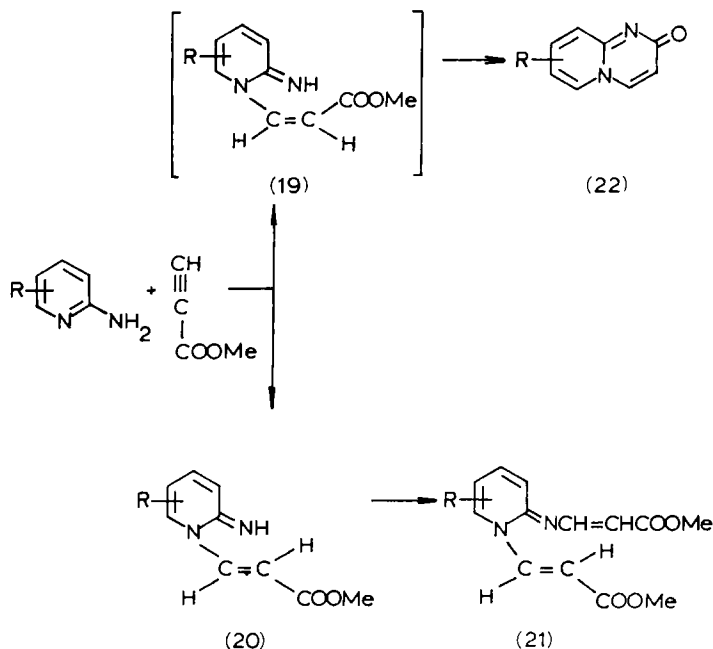
Adams and Pachter found that the reaction of 2-aminopyridine and 2-bromoacrylic acid yields a mixture of 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (18) and 3,4-dihydroimidazo[1,2-*a*]pyridine-2-carboxylic acid (17). The product ratio was dependent upon the reaction conditions.¹⁸



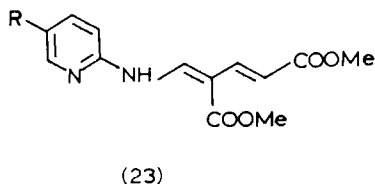
4-Methyl derivatives of 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines were prepared by Kato *et al.*¹⁹ and Potts *et al.*² by using 2-bromocrotonic acid and ethyl tetrolate, respectively.

¹⁸ R. Adams and I. J. Pachter, *J. Am. Chem. Soc.* **74**, 5491 (1952).

¹⁹ T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* **20**, 142 (1972).



Lappin^{20,21} studied the reactions of 2-aminopyridine and its monomethyl derivatives with methyl propiolate. In addition to the 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines (22), the monoadducts (20) and/or the diadducts (21) were isolated. Only the pyrido[1,2-*a*]pyrimidine was formed from 2-amino-6-methylpyridine. Lappin came to the conclusion that the addition step of the reaction is not stereospecific and that it leads to both the *Z* (19) and *E* (20) acrylates. In the next step the *Z* stereoisomer (19) readily undergoes cyclization due to its favorable geometric arrangement, thereby forming 22. The *E* acrylate (20) may react with another molecule of methyl propiolate to give the diadduct (21). Repetition of this work by Wilson and Bottomley²² led, in the case of 2-aminopyridine and 2-amino-5-methylpyridine, to the



²⁰ G. R. Lappin, *Org. Chem. Bull.* **33**, 6 (1961).

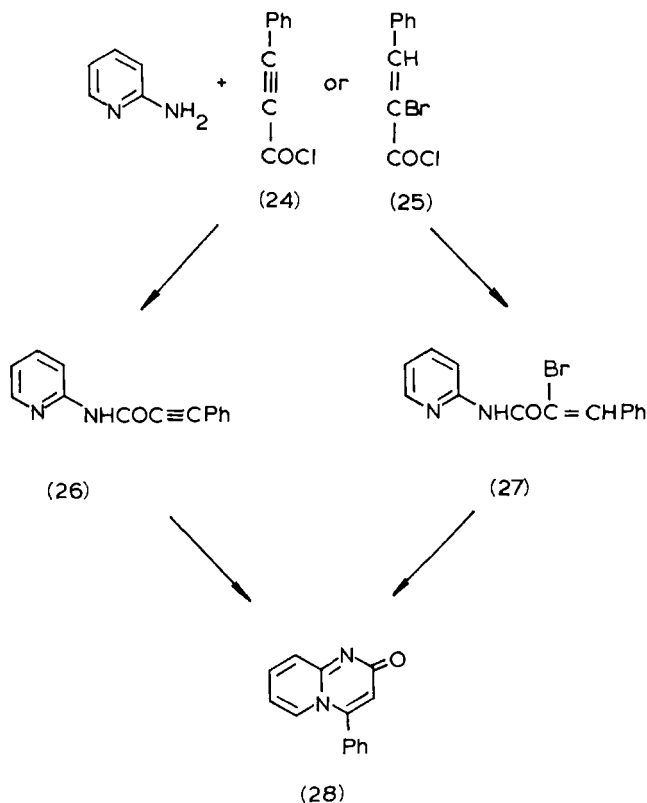
²¹ G. R. Lappin, *J. Org. Chem.* **26**, 2350 (1961).

²² J. G. Wilson and W. Bottomley, *J. Heterocycl. Chem.* **4**, 360 (1967).

isolation of a further diadduct (**23**). With the aid of ^1H NMR the trans configuration of the products (**20**, **21**, and **23**) was confirmed.

From propiolic acid and 2-aminopyridine Pachter²³ obtained 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (**18**) and the acid analog of the acrylate (**20**; R = H).

Al-Jallo and Al-Biaty²⁴ prepared 4-phenyl-2-oxo-2*H*-pyrido[1,2-*a*]-pyrimidines from 2-aminopyridines and ethyl phenylpropiolate. When the reactions were carried out in deuterium oxide, the 3-deuterated derivatives were obtained. 2-Amino-5-nitropyridine failed to react.

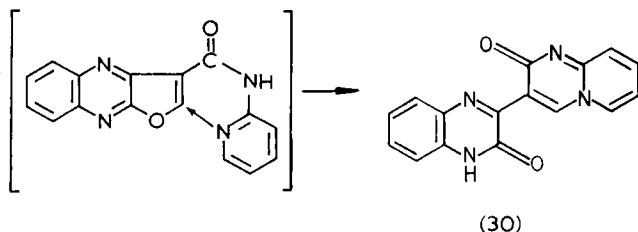
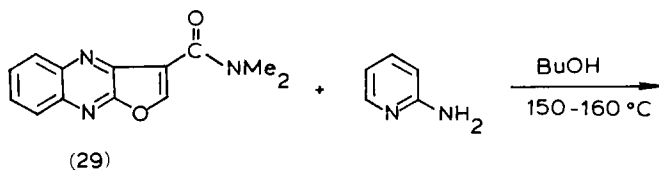


Tkachenko *et al.*²⁵ prepared 4-phenyl-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (**28**) starting from 2-aminopyridine and the acid chloride (**24** or **25**) and associated intermediates **26** or **27**.

²³ I. J. Pachter, *J. Org. Chem.* **26**, 4157 (1961).

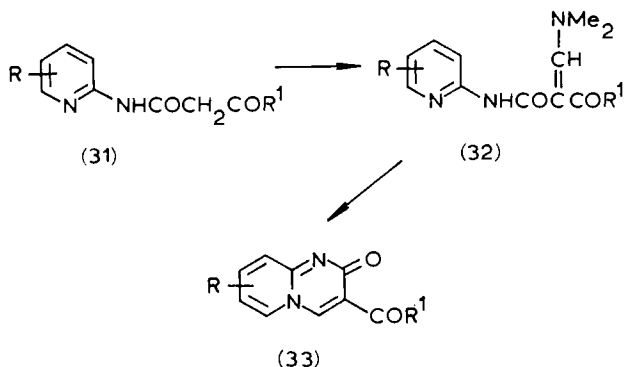
²⁴ H. N. Al-Jello and J. A. Al-Biaty, *J. Heterocycl. Chem.* **15**, 801 (1978).

²⁵ P. V. Tkachenko, A. M. Simonov, and I. I. Popov, *Khim. Geterotsikl. Soedin.*, 90 (1978) [*CA* **88**, 190727 (1978)].



By reacting furo[2,3-*b*]quinoxaline (29) with 2-aminopyridine, Kurasawa and Takada^{26,27} obtained the 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (30).

Seidel²⁸ cyclized compounds (32) derived from the amides (31) with dimethylformamide dimethyl acetal to the 3-substituted 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines (33) by heating in acetic anhydride. On this basis he corrected the conclusion of Antaki,²⁹ who had assumed that by reacting 2-amino-4-methylpyridine and ethyl ethoxymethylenecyanoacetate, the 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (33: R = 8-Me, R¹ = OEt) was produced. The product was in fact the 4-oxo isomer (36: R = 8-Me, R¹ = H, R² = COOEt).



²⁶ Y. Kurasawa and A. Takada, *Heterocycles* **14**, 611 (1980).

²⁷ Y. Kurasawa and A. Takada, *Chem. Pharm. Bull.* **28**, 3537 (1980).

²⁸ M. C. Seidel, *J. Org. Chem.* **37**, 600 (1972).

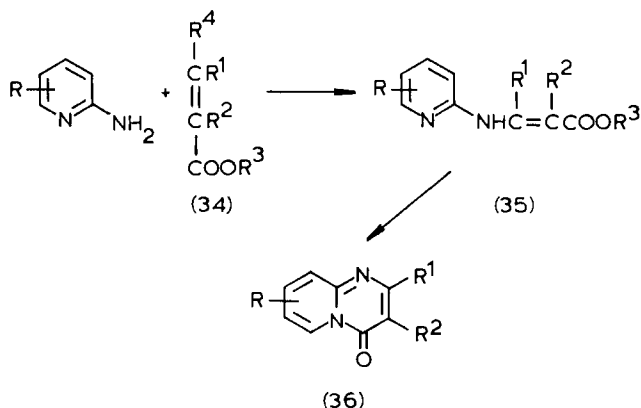
²⁹ M. Antaki, *J. Am. Chem. Soc.* **80**, 3066 (1958).

For the bicyclic product arising from the sodium ethoxide-catalyzed reaction of 2-aminopyridine and isonitrosocyanoacetate, Glushkov and Magidson³⁰ considered both the 4-amino-3-nitroso-2-oxo-2*H*- and the 2-amino-3-nitroso-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine structures, preferring the former. This structure, however, can be questioned on the basis of the patent of Kummer *et al.*³¹

The reaction product of 2-amino-4,6-diphenylpyridine-3-nitrile and ethyl acetoacetate was described by Jahine *et al.*³² as a 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine derivative. Synthesis of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (next section), however, makes the 4-oxo structure more likely.

C. 4-Oxo-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

The widely used synthetic method for the preparation of the title compounds involves the condensation of 2-aminopyridines with 1,3-bifunctional compounds (**34**) (β -oxo esters, malonates, or 2-alkoxymethylene malonates)



or with derivatives of these compounds to yield an intermediate (**35**), which is cyclized to the pyridopyrimidine (**36**) without isolation or after isolation on the action of heat, acid, or base. 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidines have also been prepared by reacting other pyridine derivatives and 1,3-bifunctional compounds, as well as by transformation of an appropriate ring system. The 6,7,8,9-tetrahydro derivatives of **36** can be prepared either by syntheses starting from tetrahydropyridines or by ring transformation of an appropriate saturated ring system.

³⁰ R. G. Glushkov and O. Yu. Magidson, *Biol. Akt. Soedin.*, 12 (1965) [*CA* **63**, 16351 (1965)].

³¹ W. Kummer, H. Köppe, H. Stähle, and A. Fügner, German Patent 2,757,929 [*CA* **91**, 140864 (1979)].

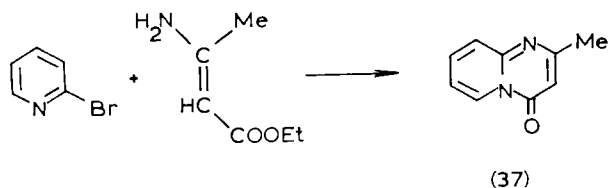
³² H. Jahine, H. A. Zaher, O. Sherif, and M. M. Fawzy, *Indian. J. Chem., Sect. B* **16B**, 889 (1978).

1. From β -Oxo Esters and Their Congeners

The first representative (37) of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was obtained by Palazzo and Tamburini³³ in 1911 from 2-aminopyridine and ethyl acetoacetate, though they believed the compound to be 4-methyl-2-oxo-1,2-dihydro-1,8-naphthyridine. Seide in 1925 recognized that the analogous reaction of 2-aminopyridine and ethyl benzoylacetate yields a pyrido[1,2-*a*]pyrimidine derivative.³⁴ He incorrectly assigned the 2-oxo-2*H* structure (28) to the product (36: $R^1 = \text{Ph}$, $R = R^2 = \text{H}$) since it was identical with the product obtained in 20% yield from 2-benzoylacetamidopyrimidine (31: $R^1 = \text{Ph}$) under acidic conditions. For the interpretation of this latter reaction see Scheme 1.

The possibility of the 4-oxo structure was first put forward by Crippa and Scevola,³⁵ but they too preferred the 2-oxo structure.

In 1951 Antaki and Petrow came to the conclusion that the poor yield of the pyrido[1,2-*a*]pyrimidines in the reaction of 2-aminopyridines and acylacetates is ascribed to a rearrangement reaction that the intermediate 2-acylacetamidopyridines undergo. This is also the reason why 4-oxo-4*H* and not 2-oxo-2*H* isomers are formed.³⁶ In order to provide support for this hypothesis, they worked out an unequivocal synthesis for 37 by reacting 2-bromopyridine and ethyl 3-aminocrotonate and found that the product was identical with that obtained from 2-acetylacetamidopyridine.



The formation of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines from 2-aminopyridines and β -oxo esters has been studied in detail by a number of workers. The works of Khitrik,³⁷ Kucherov,³⁸⁻⁴⁰ and Shur and Israelstam⁴¹ are of special interest. Khitrik found that the reaction of 2-aminopyridine and ethyl acetoacetate yields 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (41: $R = \text{H}$)

³³ F. C. Palazzo and A. Tamburini, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* [5] **20**, 37 (1911) [*CA* **5**, 1586 (1911)].

³⁴ O. Seide, *Chem. Ber.* **58**, 352 (1925).

³⁵ G. B. Crippa and E. Scevola, *Gazz. Chim. Ital.* **67**, 327 (1937).

³⁶ H. Antaki and V. Petrov, *J. Chem. Soc.*, 551 (1951).

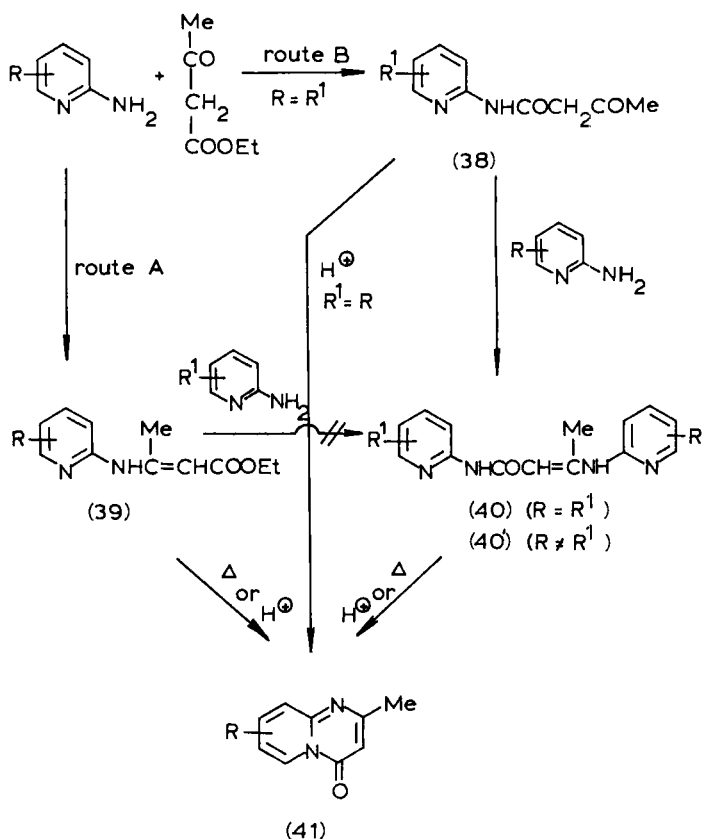
³⁷ S. N. Khitrik, *J. Gen. Chem. USSR* **9**, 1109 (1939) [*CA* **33**, 8615 (1939)].

³⁸ V. F. Kucherov, *J. Gen. Chem. USSR* **20**, 1890 (1950) [*CA* **45**, 2951 (1951)].

³⁹ V. F. Kucherov, *J. Gen. Chem. USSR* **21**, 1145 (1951) [*CA* **46**, 5043 (1952)].

⁴⁰ V. F. Kucherov, *J. Gen. Chem. USSR* **21**, 1249 (1951) [*CA* **46**, 8112 (1952)].

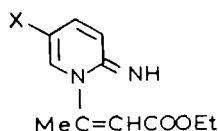
⁴¹ M. Shur and S. S. Israelstam, *J. Org. Chem.* **33**, 3015 (1968).



SCHEME 1

at 150–160°C, crotonic amide (40: R = R¹ = H) at 130°C, and 2-acetylacetamidopyridine (38: R = H) at 100°C. No product of type 39 was obtained under any of the above conditions. The crotonic amide (40: R = R¹ = H) was also obtained when 2-aminopyridine was reacted with 2-acetylacetamidopyridine. The crotonic amide cyclized on the action of heat or acid, forming the 4-oxo-4H-pyrido[1,2-a]pyrimidine (41: R = H), whereas 2-acetylacetamidopyridine cyclized only on the action of acid (concentrated sulfuric acid).³⁷

Kucherov^{38–40} studied the reaction of 2-amino-5-halopyridines with ethyl acetoacetate and obtained 4-oxo-4H-pyrido[1,2-a]pyrimidines (41: R = 7-halo) in 20–25% yield at 190–195°C, and crotonic amides (40: R = R¹ = 5-halo) in 60–65% yield and crotonates (39: R = 5-halo) in 1–2% yield at 140–170°C. He assigned the 2-oxo-4H structure to the pyridopyrimidines (41). The crotonate (39) was described correctly in his first paper, but later he changed the structure to 42.



(42)

Kucheroov reacted 2-acetylacetamidopyridines (**38**: R = halo) with 2-amino-5-halopyridines. In this way crotonic amides (**40**) with different halogen atoms in the pyridine rings were synthesized. Ring closure of these compounds was not studied. Crotonates (**39**) and 2-amino-5-halopyridines did not yield crotonic amides (**40**).

The crotonates (**39**) were cyclized by Kucheroov to the pyrido[1,2-*a*]-pyrimidines by being heated in water or being treated with concentrated sulfuric acid at room temperature. The crotonic amides (**40**) cyclized above their melting point or in concentrated sulfuric acid, whereas the 2-acetylacetamidopyridines (**38**) did so only in concentrated sulfuric acid.

Shur and Israelstam⁴¹ applied polyphosphoric acid to cause ring closure. Although the crotonates (**39**) and the crotonic amides (**40**) cyclized almost quantitatively to 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**41**), cyclization of the 2-acetylacetamidopyridines (**38**) could only be achieved in less than 50% yield. When one additional equivalent of 2-aminopyridine was included in the reaction mixture of **38**, the yield of **41** increased to over 80%. When the ring closure was carried out from crotonic amides (**40**) containing different 2-aminopyridine moieties, the resulting 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines bore the substituent of the pyridine of the enamine part of the crotonic amide. The authors proposed that the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**41**) may arise from 2-aminopyridines and ethyl acetoacetate in polyphosphoric acid via two pathways (see Scheme 1). 2-Amino-3-methylpyridine and 2-amino-3,5-dibromopyridine react via pathway A and 2-aminopyridine, 2-amino-4-, -5-, and -6-methylpyridines react via pathway B, whereas 2-amino-5-chloro- and 5-bromopyridines may react via both pathways.

2-Aminopyridines were reacted with β -oxo esters, primarily ethyl acetoacetate and ethyl benzoylacetate, by heating above the melting point,^{33,37,38,42-49} occasionally in the presence of a few drops of hydro-

⁴² M. S. Kondakova and Ya. L. Goldfarb, *J. Gen. Chem. USSR* **10**, 1065 (1940) [*CA* **35**, 4021 (1941)].

⁴³ M. Khalifa, *Bull. Fac. Pharm.* **1**, 149 (1961-1962) [*CA* **61**, 5643 (1964)].

⁴⁴ A. Mendel, *J. Heterocycl. Chem.* **9**, 935 (1972).

⁴⁵ H. L. Yale, B. Toeplitz, J. E. Gougoutas, and M. Puer, *J. Heterocycl. Chem.* **10**, 123 (1973).

⁴⁶ H. L. Yale and J. T. Sheehan, *J. Heterocycl. Chem.* **10**, 143 (1973).

⁴⁷ H. L. Yale, *J. Heterocycl. Chem.* **11**, 739 (1974).

⁴⁸ H. L. Yale and E. R. Spitzmiller, *J. Heterocycl. Chem.* **14**, 637 (1977).

⁴⁹ H. Fujita, Y. Shimaji, S. Kojima, H. Nishino, K. Kamoshita, K. Endo, S. Kobayashi, S. Kummakura, and Y. Sato, *Senkyo Kenkyusho Nempo* **29**, 75 (1977) [*CA* **89**, 43299 (1978)].

chloric acid^{35,50} or by heating in solvents with high boiling points, such as dimethylformamide,⁴⁴ trichlorobenzene,⁴⁸ and diethylbenzene.^{46,51} These methods usually gave yields of less than 30–40% and the ring closure was accompanied by side reactions.

Mendel⁴⁴ found that reaction of 2-aminopyridine-3-carboxylic acid with ethyl acetoacetate or ethyl benzoylacetate gave rise to a decarboxylated product (**36**: R¹ = Me, Ph; R = R² = H), whereas with ethyl 4,4,4-trifluoroacetoacetate, the product was ethyl 2-aminopyridine-3-carboxylate. Yale⁵¹ obtained 3-benzoyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine in 4–5% yield from 2-amino-3-methylpyridine and ethyl benzoylacetate in diethylbenzene.

Another version of the reaction of 2-aminopyridines and β -oxo esters is the isolation and cyclization of the intermediates of type **38** or **39**. Compounds of type **38** were cyclized in concentrated sulfuric acid at ambient³⁷ or elevated temperature,^{34,36,38,43,52,53} in polyphosphoric acid,⁴¹ or in toluene in the presence of *p*-toluenesulfonic acid.⁴⁸ Cyclization of the acrylates (**39**) was carried out by heating without solvent⁴⁷ or in solution in water,^{39,40} diethylbenzene,⁴⁷ or toluene in the presence of *p*-toluenesulfonic acid.⁴⁸ Cyclization also took place when **39** was chromatographed on a silica gel column.⁴⁸

The one-step procedure, i.e., reaction of 2-aminopyridines and β -oxo esters in the presence of an acid, generally gave higher yields. Thus, depending on the starting materials, the yields achieved were 10–60% in methyl cellosolve in the presence of *p*-toluenesulfonic acid,^{48,54–60} 30–70% in acetic acid,^{49,61–64} and 44–98% in polyphosphoric acid^{8,41,49,64–73} or in a

⁵⁰ C. R. Hauser and M. J. Weiss, *J. Org. Chem.* **14**, 453 (1949).

⁵¹ H. L. Yale, *J. Heterocycl. Chem.* **15**, 1047 (1978).

⁵² A. E. Chichibabin, German Patent 451,733; *Fridlaender* **15**, 335 (1928).

⁵³ I. T. Barnish, C. R. Hauser, and J. F. Wolfe, *J. Org. Chem.* **33**, 2116 (1968).

⁵⁴ H. L. Yale, *J. Heterocycl. Chem.* **12**, 427 (1975).

⁵⁵ H. L. Yale and E. R. Spitzmiller, U.S. Patent 3,898,224 [CA **83**, 179105 (1975)].

⁵⁶ H. L. Yale, U.S. Patent 3,929,787 [CA **84**, 105645 (1976)].

⁵⁷ H. L. Yale, U.S. Patent 3,935,197 [CA **85**, 21430 (1976)].

⁵⁸ H. L. Yale and E. Spitzmiller, *J. Heterocycl. Chem.* **13**, 797 (1976).

⁵⁹ H. L. Yale and J. T. Sheehan, U.S. Patent 4,022,897 [CA **87**, 85040 (1977)].

⁶⁰ G. Doria, C. S. Romeo, P. Sberze, M. Tibolla, and M. L. Corno, German Patent 3,015,738 [CA **94**, 175150 (1981)].

⁶¹ Y. Yakoyama, K. Shibata, O. Fujii, and E. Iwamoto, *Bull. Chem. Soc. Jpn.* **48**, 591 (1975).

⁶² Y. Yokoyama, K. Shibata, O. Fujii, and E. Iwamoto, *Toyo Soda Kenkyu Hokoku* **19**, 71 (1975) [CA **85**, 125771 (1976)].

⁶³ C. F. Schwender, R. S. Brooks, and D. J. Herning, *J. Med. Chem.* **22**, 114 (1979).

⁶⁴ H. Böhme and K. H. Weisel, *Arch. Pharm. (Weinheim. Ger.)* **309**, 959 (1976).

⁶⁵ H. J. Willenbrock, H. Wamhoff, and H. Korte, *Justus Liebigs Ann. Chem.*, 103 (1973).

⁶⁶ Y. Sato, H. Fujita, H. Takagi, and K. Kamoshita, German Patent 2,526,983 [CA **84**, 135712 (1976)].

⁶⁷ H. Böhme and K. H. Weisel, *Chem. Ber.* **109**, 2908 (1976).

phosphoryl chloride–polyphosphoric acid mixture.^{71–80} Polyphosphoric acid was also replaced by ethyl polyphosphate.^{81–83}

2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**37**) was prepared in 90% yield from 2-aminopyridinium iodide and ethyl acetoacetate in pyridine at reflux temperature.² The yield dropped to 20% when 1,2-diaminopyridinium iodide was used instead of 2-aminopyridine.²

The product obtained from 2-aminopyridine and ethyl 2-methylacetoacetate in ethyl polyphosphate was described by Mullock *et al.*⁸¹ as 1,8-naphthyridine, but it was shown later by Bowden and Brown⁸² to be 2,3-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**36**; R¹ = R² = Me, R = H). 2-Acetylbutyrolactone (**43**) and its 5-substituted derivatives have also been used as β -oxo ester component^{49,65,83–85}.

2-Aminopyridines and the lactone (**43**) in polyphosphoric acid at 160°C gave 3-(2-hydroxyethyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**44**). At lower temperature (120°C) the furan derivative (**46**) was formed.⁶⁵ When effected with phosphoryl halides (POCl₃ or POBr₃), reaction of 2-aminopyridines and **43** afforded products of type **44** where the hydroxyl group was replaced by a halogen atom.^{49,83,85}

⁶⁸ H. Böhme and K. H. Weisel, *Arch. Pharm. (Weinheim, Ger.)* **310**, 26 (1977).

⁶⁹ S. Carboni, A. Da Settimo, P. L. Ferrarini, and O. Livi, *Farmaco, Ed. Sci.* **33**, 315 (1978).

⁷⁰ L. E. J. Kennis and J. C. Mertens, European Patent 37,265 [CA **96** 122814 (1982)].

⁷¹ F. Fülöp, I. Hermecz, Z. Mészáros, G. Dombi, and G. Bernáth, *J. Heterocycl. Chem.* **16**, 457 (1979).

⁷² J. Knoll, Z. Mészáros, I. Hermecz, F. Fülöp, G. Bernáth, S. Virág, G. Nagy, and P. Szentmiklósi, German Patent 2,835,004 [CA **91**, 5243 (1979)]; U.S. Patent 4,291,036 [CA **96**, 35295 (1981)].

⁷³ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,195 [CA **91**, 57053 (1979)].

⁷⁴ Z. Mészáros, J. Knoll, and P. Szentmiklósi, British Patent 1,209,946 [CA **75**, 5939 (1971)].

⁷⁵ Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, *Arzneim.-Forsch.* **22**, 815 (1972).

⁷⁶ Z. Mészáros, J. Knoll, and P. Szentmiklósi, HUNG. TELJES **4910** [CA **78**, 29806 (1973)].

⁷⁷ Z. Mészáros, J. Knoll, and P. Szentmiklósi, HUNG. TELJES **4911** [CA **78**, 43539 (1973)].

⁷⁸ Z. Mészáros, I. Hermecz, G. Nagy, S. Virág, L. Vasvári-Debreczy, A. Horváth, F. Bognár, Á. Dávid, and G. Horváth, HUNG. TELJES **10957** [CA **85**, 108662 (1976)].

⁷⁹ I. Hermecz, Z. Mészáros, L. Vasvári-Debreczy, A. Horváth, G. Horváth, and M. Pongor-Csákvári, *J. C. S. Perkin I*, 789 (1977).

⁸⁰ F. Fülöp, G. Bernáth, I. Hermecz, and Z. Mészáros, *Pharmazie* (to be published).

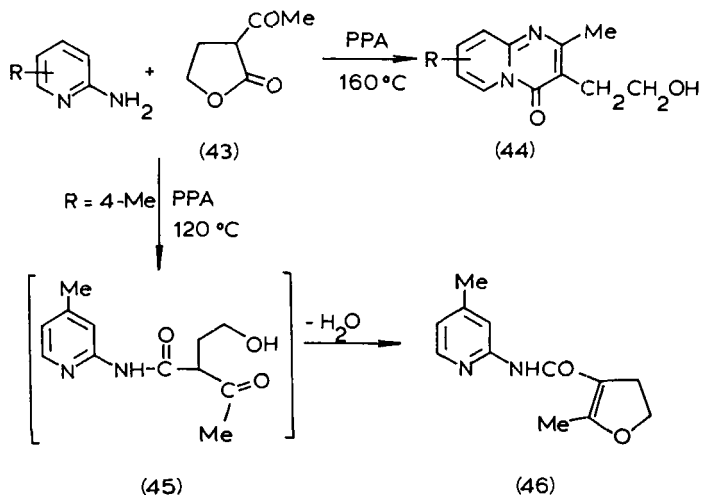
⁸¹ E. B. Mullock, R. Searby, and H. Suchitzky, *J. Chem. Soc. C*, 829 (1970).

⁸² K. Bowden and T. H. Brown, *J. Chem. Soc. C*, 2163 (1971).

⁸³ Y. Sato, H. Fujita, H. Takagi, and K. Kamoshida, Japan Kokai 76/146,497 [CA **87**, 68406 (1977)].

⁸⁴ H. Wamhoff and F. Korte, *Synthesis*, 151 (1972).

⁸⁵ Y. Morisawa and Y. Sato, Japan Kokai 75/149,698 [CA **85**, 21423 (1976)].



When the 5-phenyl derivative of **43** was used, a mixture of 3-(2-phenyl-2-chloroethyl)- and 3-(2-phenylvinyl)-8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was obtained.⁴⁹ Depending on the conditions, reaction of 2-aminopyridines with 2-acetyl-4-chloromethylbutyrolactone (**47**) led to a variety of bicyclic products (**48–54**) (Scheme 2).^{49,83} Reaction of 2-aminopyridines with the acid chloride (**55**) yielded 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**56**) and traces of the amides of type **57**. From 2-amino-6-methylpyridine, only the amide (**57**; R = 6-Me) was formed.⁸⁶

Böhme and Weisel obtained 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**59**) from 2-aminopyridine and ethyl 2-chloroacetoacetate. The yield was 10% in toluene in the presence of *p*-toluenesulfonic acid, 30% in acetic acid, and 59% in polyphosphoric acid. The triethylamine-catalyzed reaction in benzene led to the imidazo[1,2-*a*]pyridine **58**.⁶⁴ 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**59**) was also prepared from 2-aminopyridine and 2-chloro-3-oxobutyronitrile.⁶⁷

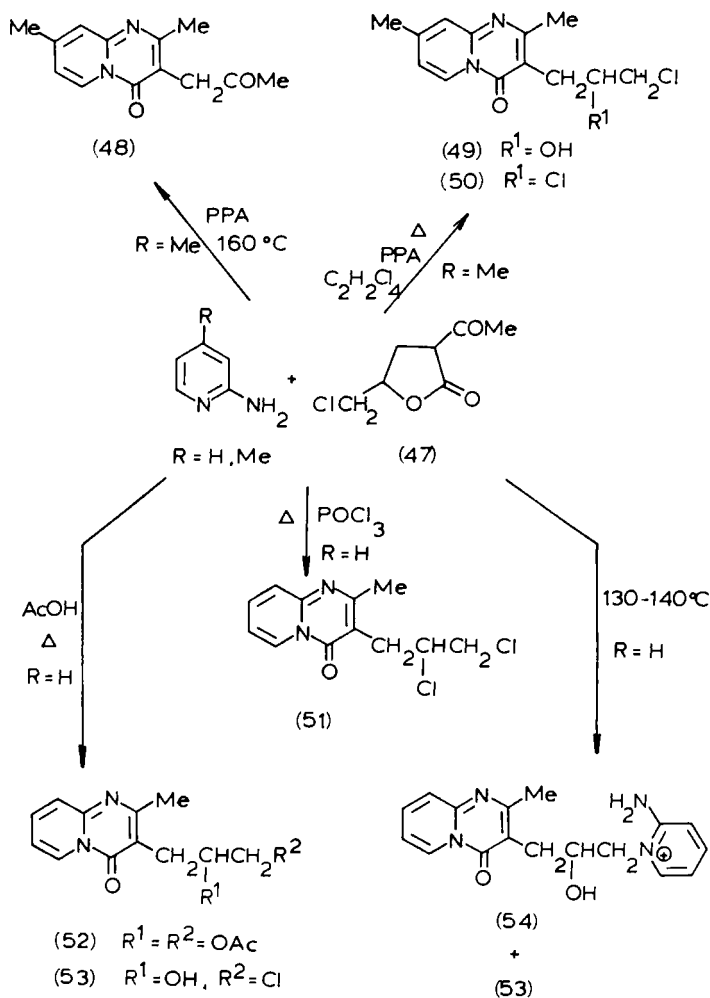
Instead of β -oxo esters, 3-aminoacrylates (**60**) have also been applied. Reaction of **60** with 2-bromopyridines in the presence of copper bronze,^{19,36} or with 2-aminopyridines at 180–270°C,^{36,46,48,56,59,87–89} or in the presence

⁸⁶ M. A. Corbeil, M. Curcumelli-Rodostamo, R. J. Fanning, B. A. Graham, M. Kulka, and J. B. Pierce, *Can. J. Chem.* **51**, 2650 (1973).

⁸⁷ H. Antaki, *J. Org. Chem.* **27**, 1371 (1962).

⁸⁸ H. L. Yale and J. T. Sheehan, German Patent 2,245,363 [*CA* **78**, 159648 (1973)].

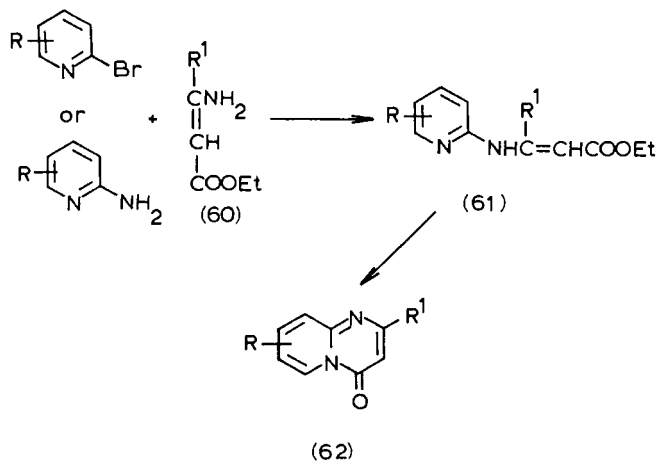
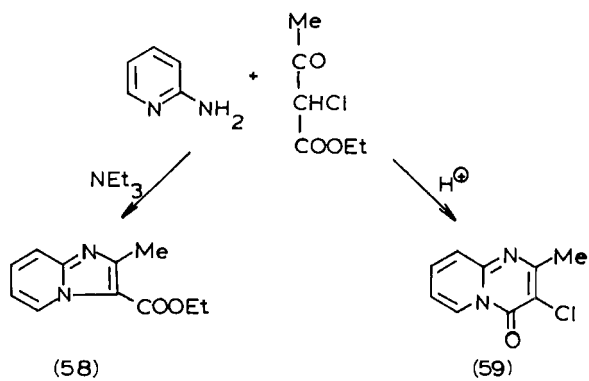
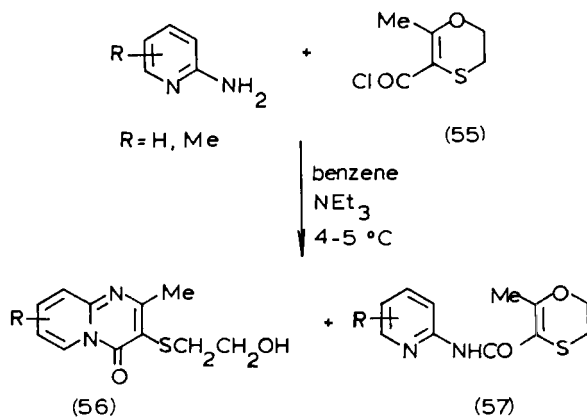
⁸⁹ H. L. Yale and E. R. Spitzmiller, *J. Heterocycl. Chem.* **14**, 1419 (1977).



SCHEME 2

of diethylbenzene at reflux temperature⁵⁴ gave 4-oxo-4H-pyrido[1,2-*a*]pyrimidines (**62**) in good yields. At lower temperature the intermediate (**61**) could be isolated in refluxing toluene.⁸⁹

From 2-amino-6-methylpyridine and ethyl 3-aminocrotonate the expected 2,6-dimethyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine was not obtained, but instead a urea derivative is formed.³⁶ Ethyl acetoacetate has also been replaced



by diketene.^{19,45-47,90-93} Depending on the reaction conditions, the product was 2-acetylacetamidopyridine (38) and/or 2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (41).

Allen *et al.*⁹⁰ suggested that 2-aminopyridine and 2-amino-3-methylpyridine reacted with diketene in ether to give 2-acetylacetamidopyridine (38; R = H, 3 = Me). Later Shur and Israelstam⁴¹ demonstrated that the product formed from 2-amino-3-methylpyridine was in fact 2,9-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (41; R = 9-Me).

Stöckelmann *et al.* reacted 2-amino-3-methylpyridine and 2-amino-4-methylpyridine with diketene in water. The 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine structure was assigned to the products, reportedly obtained in 90 and 97% yields.⁹² Kato *et al.*¹⁹ and Yale *et al.*⁴⁵ subsequently demonstrated that the products were 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines and the yields were not higher than 16%.

Yale and Spitzmiller^{48,93} reacted a variety of 2-aminopyridines with diketene in toluene and obtained 2-acetylacetamidopyridines (38). In some cases the intermediates (38) were not isolated but were transformed upon further heating in the presence of *p*-toluenesulfonic acid to 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (41).⁴⁸

Kato *et al.*⁹⁴ reported that 2-amino-6-methylpyridine and diketene did not yield 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines but instead yielded 2-acetylacetamido-6-methylpyridine and pyridone or pyrone derivatives. 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (47) and its 8-methyl derivative have also been prepared from 2-aminopyridine and 2-amino-4-methylpyridine with *N,N*-dimethyl-3-aminocrotonamide⁹⁵ or with acetoacetamide⁴⁵ in yields of 5 and 39%, respectively.

2. From Malonic Esters and Their Congeners

Chichibabin⁹⁶ prepared the first representatives of pyridopyrimidines of type 63. Instead of assuming the 63 zwitterionic form, Chichibabin used the 2,4-dioxo structure and named the compounds malonyl- α -aminopyridines.

⁹⁰ C. F. H. Allen, J. Van Allen, and C. V. Wilson, *J. Am. Chem. Soc.* **66**, 1805 (1944).

⁹¹ T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma, and M. Oizumi, *Chem. Pharm. Bull.* **13**, 910 (1964).

⁹² G. Stöckelmann, H. Specker, and W. Riepe, *Chem. Ber.* **102**, 455 (1969).

⁹³ H. L. Yale and E. R. Spitzmiller, *J. Heterocycl. Chem.* **14**, 241 (1977).

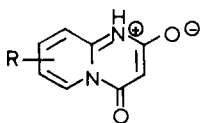
⁹⁴ T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* **20**, 133 (1972).

⁹⁵ H. Brederick, R. Gompper, K. Klemm, and B. Foehlich, *Chem. Ber.* **94**, 3119 (1961).

⁹⁶ A. E. Chichibabin, *Chem. Ber.* **57**, 1168 (1924).

It remained inexplicable to him why 2-aminopyridine and diethyl diethylmalonate failed to provide the 3,3-diethyl derivative under the same conditions. Crippa and Scevola³⁵ also attempted to prepare the 3,3-diethyl derivative by reacting 2-aminopyridine with diethylmalonyl chloride in pyridine at room temperature, but the reaction yielded a malonamide derivative. For the structure of Chichibabin's product (**63**: R = H), see Section IV of this chapter.

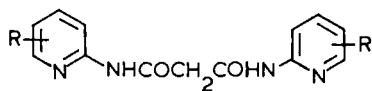
The reaction of 2-aminopyridines and diethyl malonate was studied in detail by Lappin *et al.*⁹⁷ and Ingalls and Popp.⁹⁸ Lappin *et al.* carried out the reaction in the melt at 210–220°C or in a high-boiling solvent (Dowtherm A) at 240–250°C. Depending on the substituents of the starting material noncyclized products of type **64** and/or **65** and/or bicyclic products, the pyrido[1,2-*a*]pyrimidines (**63**) or the naphthyridines (**66**) were isolated.⁹⁷



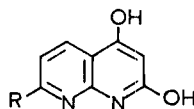
(63)



(64)



(65)



(66)

Lappin *et al.* explained the formation of the 1,8-naphthyridines (**66**) by the effect of the substituent at C-6, which sterically hinders the ring closure onto the pyridine nitrogen and activates position 3 through its electron-donating effect. For interpretation of the formation of 1,8-naphthyridines, see also Section II,C,3.

Whereas Kucherov and co-workers⁹⁹ had previously obtained only noncyclized products of type **64** and **65** from the reaction of 2-amino-5-halopyridines and diethyl malonate, Lappin *et al.*⁹⁷ succeeded in cyclizing the 5-halo (Cl and Br) derivatives of **64** to pyrido[1,2-*a*]pyrimidines (**63**) by applying semimicro sublimation to induce cyclization.

Ingalls and Popp⁹⁸ reacted 2-aminopyridines with diethyl malonate at 200°C. 2-Amino-3-nitropyridine failed to react, but in contrast to the findings

⁹⁷ G. R. Lappin, Q. R. Peterson, and C. E. Wheeler, *J. Org. Chem.* **15**, 377 (1950).

⁹⁸ E. A. Ingalls and F. D. Popp, *J. Heterocycl. Chem.* **4**, 523 (1967).

⁹⁹ N. F. Kucherova, V. F. Kucherov, and K. A. Kocheshkov, *J. Gen. Chem. USSR* **16**, 1706 (1946) [*CA* **41**, 6243 (1947)].

of Kuchеров and co-workers,⁹⁹ 2-amino-5-nitropyridine furnished the non-cyclized product (**64**). The absence of cyclization was explained by the deactivating effect of the nitro group. The 5-halopyridines gave only non-cyclized products (**65**) and 2-amino-6-methylpyridine and 2-aminoquinazoline yielded noncyclized products of type **64**, whereas from 2-amino-4,6-dimethylpyridine both **64** and **65** were obtained. In all the other cases the expected pyrido[1,2-*a*]pyrimidines (**63**) resulted.

The reaction of 2-aminopyridines with diethyl malonate or monosubstituted malonates has been investigated by many other workers. Cyclizations were carried out thermally, either without solvents^{43,51,52,87,96,98,100-110} or in high-boiling solvents,^{63,97,111} or on the action of acid^{47,75-77} or base.¹¹²

From 2-amino-6-methylpyridine and monosubstituted malonates Buu Hoi and Declercq¹⁰⁰ obtained 3-substituted 1,8-naphthyridines of type **66**, and from 2-aminopyridine they obtained 3-substituted pyrido[1,2-*a*]pyrimidines of type **63** (R = H).

Schulte and Witt¹⁰³ reported that reaction that of 2-aminopyridine and 2-amino-4-methylpyridine with diethyl propargylmalonate produces a tricyclic product (**67**).

The pyrido[1,2-*a*]pyrimidines (**63**) were obtained by Shur and Israelstam by reacting 2-aminopyridines and diethyl malonate in polyphosphoric acid at 160–170°C. 2-Aminopyridine and diethyl malonate at 130°C gave the diamide (**65**; R = H), which could then be cyclized in polyphosphoric acid at 160°C to pyrido[1,2-*a*]pyrimidine (**63**; R = H). From 2-amino-6-methylpyridine and 2-amino-5-halopyridines at temperatures up to 170°C, only the diamides (**66**) were isolated.⁴¹

Mészáros *et al.* reacted 2-amino-6-methylpyridine with diethyl malonate in a mixture of phosphoryl chloride and polyphosphoric acid and isolated

¹⁰⁰ Nh. Pg. Buu-Hoi and M. Declercq, *Recl. Trav. Chim. Pays-Bas* **73**, 376 (1954).

¹⁰¹ J. T. Plati and W. Wenner, U.S. Patent 2,698,846 [CA **50**, 1093 (1956)].

¹⁰² Roche Products Ltd., British Patent 746,437 [CA **51**, 502 (1957)].

¹⁰³ K. E. Schulte and J. Witt, *Arch. Pharm. (Weinheim. Ger.)* **291**, 298 (1958).

¹⁰⁴ R. E. Allen, Belgian Patent 621,702 [CA **59**, 12819 (1963)].

¹⁰⁵ B. Tumor, A. S. Sadykov, and Sh. Sharipova, *Uzb. Khim. Zh.* **7**, 64 (1963) [CA **59**, 15281 (1963)].

¹⁰⁶ A. Kotarska, *Lodz. Tow. Nauk. Pr. Wydz.* **3** **12**, 93 (1967) [CA **71**, 112878 (1969)].

¹⁰⁷ T. Kappe, M. A. A. Chirazi, and E. Ziegler, *Monatsh. Chem.* **103**, 426 (1972).

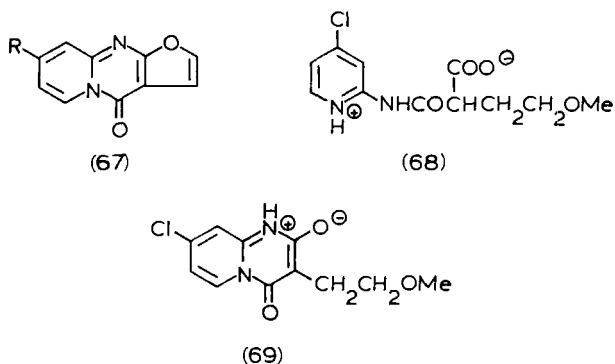
¹⁰⁸ J. Perronnet and L. Taliani, German Patent 2,345,762 [CA **81**, 3964 (1974)].

¹⁰⁹ D. W. Heseltine and L. G. S. Brooker, U.S. Patent 3,213,089 [CA **64**, 3747 (1966)].

¹¹⁰ A. G. Terzyan and Zh. G. Akopyan, *Sint. Geterotsikl. Soedin., Akad. Nauk Arm. SSR Tonkoi Organ. Khim.*, 60 (1964) [CA **65**, 18580 (1966)].

¹¹¹ J. Klosa, *J. Prakt. Chem.* **26**, 150 (1964).

¹¹² R. Urban, M. Grosjean, and W. Arnold, *Helv. Chim. Acta* **53**, 905 (1970).



2-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidine in 9% yield. Ring closure was accompanied by hydroxy to chloro exchange.⁷⁵⁻⁷⁷

Urban *et al.* effected the ring closure of 2-aminopyridines and diethyl malonate in ethanolic sodium ethoxide. 2-Amino-4-chloropyridine and diethyl 2-methoxyethyl malonate gave only the noncyclized product (68), which was then transformed in a separate reaction with *N,N'*-dicyclohexylcarbodiimide in dimethylformamide at room temperature to the pyrido[1,2-a]pyrimidine (69).¹¹² Besides diethyl malonates, the active esters^{107,108,113-117} and malonyl dichlorides^{52,118,119} have also been used as reaction partners of 2-aminopyridines.

Dvortsák *et al.*¹¹⁷ found that bis(pentachlorophenyl)malonates and 2-aminopyridine formed the pyrido[1,2-a]pyrimidines (63; R = H) even at room temperature in acetone in the presence of triethylamine. By the reaction of bis(2,4,6-trichlorophenyl)malonates with 2-(monosubstituted amino)pyridines at 160–175°C, the 1-substituted derivatives of the pyrido[1,2-a]pyrimidines (63) were prepared.¹¹⁴⁻¹¹⁶

Instead of malonic esters, carbon suboxide^{115,120-123} has also been used to react with 2-aminopyridine. The first reaction of this type was carried out

¹¹³ E. Ziegler, H. Junek, and H. Biemann, *Monatsh. Chem.* **92**, 727 (1961).

¹¹⁴ T. Kappe, P. F. Fritz, and E. Ziegler, *Monatsh. Chem.* **102**, 412 (1971).

¹¹⁵ T. Kappe and W. Lube, *Monatsh. Chem.* **102**, 781 (1971).

¹¹⁶ G. Schindler, D. Furtuopulos, and T. Kappe, *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **31B**, 500 (1976).

¹¹⁷ P. Dvortsák, G. Resofszki, M. Huhn, L. Zalántai, and I. Á. Kiss, *Tetrahedron* **32**, 2117 (1976).

¹¹⁸ M. Khalifa and Y. M. Abou-Zeid, *Bull. Fac. Pharm.* **1**, 159 (1961–1962) [*CA* **61**, 5643 (1964)].

¹¹⁹ M. Khalifa, *Bull. Fac. Pharm.* **1**, 165 (1961–1962) [*CA* **61**, 5643 (1964)].

¹²⁰ E. Ziegler and R. Wolf, *Monatsh. Chem.* **93**, 1441 (1962).

¹²¹ L. B. Dashkevich and E. N. Kuvaeva, *Khim Geterotsikl. Soedin., Sb.* **1**, 221 (1967) [*CA* **70**, 87743 (1969)].

by Pauw,¹²⁴ who was unsuccessful in working up the reaction mixture. Carrying out the reaction in ether at -70°C , Ziegler and Wolf¹²⁰ isolated the diamide (**65**: R = H) and the pyrido[1,2-*a*]pyrimidine (**63**: R = H).

The expected pyrido[1,2-*a*]pyrimidines (**63**) were prepared from carbon suboxide and 2-aminopyridines, including 2-amino-6-methylpyridine at room temperature.¹²¹

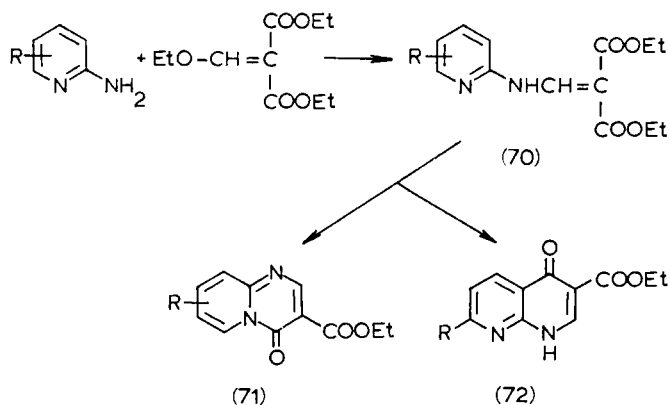
2-(Monosubstituted amino)pyridine and carbon suboxide in ether furnished 1-substituted derivatives of pyrido[1,2-*a*]pyrimidines (**63**).^{115,122,123} With aluminum chloride as a catalyst, yields were almost quantitative.¹²²

Carbon subsulfide and 2-aminopyridine gave polycondensed products instead of the dithio derivative of **63** (R = H).¹²⁵

3. From 2-Alkoxyethylenemalonates,

2-Alkoxyethylene- β -oxo Esters, and Their Congeners

A third type of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**71**) was prepared by Lappin,¹²⁶ who reacted 2-aminopyridines with ethoxymethylene malonate and cyclized the resulting condensed products (**70**) in Dowtherm A at 250°C . When the intermediates (**70**) were unsubstituted at position 6, the products were pyrido[1,2-*a*]pyrimidines (**71**), whereas from the 6-substituted intermediates (**70**: 6-R \neq H), 1,8-naphthyridines (**72**) were isolated. Prior to



¹²² K. T. Potts and M. Sorm, *J. Org. Chem.* **36**, 8 (1971).

¹²³ T. Kappe and E. Ziegler, *Angew. Chem.* **86**, 529 (1974).

¹²⁴ E. A. Pauw, *Recl. Trav. Chim. Pays-Bas* **55**, 216 (1936).

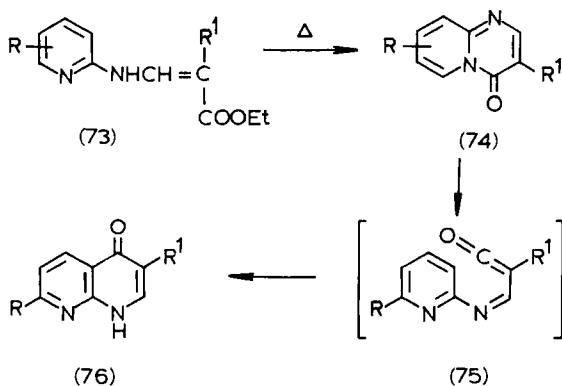
¹²⁵ W. Stadlbauer, T. Kappe, and E. Ziegler, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **33B**, 89 (1978).

¹²⁶ G. R. Lappin, *J. Am. Chem. Soc.* **70**, 3348 (1948).

Lappin's publication, 1,8-naphthyridine (**72**; $R = \text{NH}_2$) was obtained under similar conditions from the 6-amino derivative of **70** by Adams *et al.*¹²⁷ The special behavior of the 6-substituted derivatives of **70** was ascribed by Lappin¹²⁶ to the steric hindrance effect of the 6-substituent. Some later results,^{29,128} however, contradicted Lappin's concept. On vacuum distillation of the 2-(6-methyl-2-pyridylaminomethylene)acetoacetate and -cyanoacetate, Antaki did not obtain the 1,8-naphthyridines but instead the 3-substituted 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines.²⁹ By the thermal ring closure of **70** ($R = 5\text{-CONH}_2$) Richardson and McCarty¹²⁸ obtained a product described as a 1,8-naphthyridine of type **72**.

In their studies of the thermal cyclization of the malonates (**70**) and acrylates (**73**), Hermecz and co-workers^{79,129} established that cyclization of these compounds takes place at the pyridine nitrogen, but depending on the position and the nature of the substituents R and R^1 , the resulting 6-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**74**; $6\text{-}R \neq \text{H}$) may transform into the 1,8-naphthyridines (**76**) under the conditions of the ring closure. Ring transformation probably proceeds via the iminoketene (**75**).¹³⁰ The malonates (**70**), acrylates (**73**) and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**74**), where the 6-position of the pyridine ring was unsubstituted, failed to produce 1,8-naphthyridines.⁷⁹

During reinvestigation of the experiments of Richardson and McCarty,¹²⁸ Hermecz *et al.*⁷⁹ demonstrated that the product of the thermal cyclization of **70** ($R = 5\text{-CONH}_2$) was not 1,8-naphthyridine, but 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**71**; $R = 7\text{-CONH}_2$).

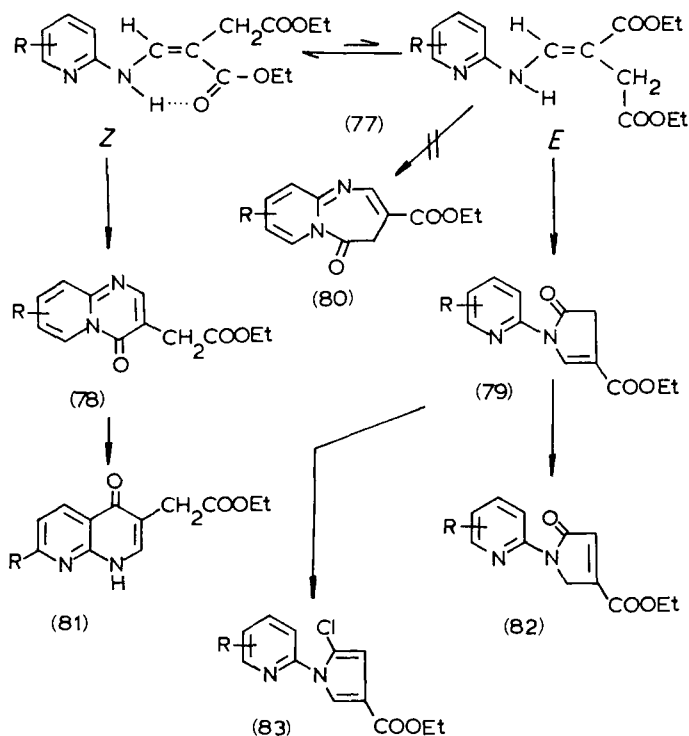


¹²⁷ J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, and C. R. Hauser, *J. Am. Chem. Soc.* **68**, 1317 (1946).

¹²⁸ J. A. Richardson and F. J. McCarty, *J. Med. Chem.* **15**, 1203 (1972).

¹²⁹ Z. Mészáros and I. Hermecz, *Tetrahedron Lett.*, 1019 (1975).

Vasvári-Debreczy *et al.* studied the ring closure of the succinates (77) under various conditions, e.g., in Dowtherm A at 250°C,^{130–133} in a phosphoryl chloride–polyphosphoric acid mixture^{132–134} at 110–120°C, and in ethanolic sodium ethoxide at room temperature.^{133–135} The authors expected various cyclic products: pyrido[1,2-*a*]pyrimidines (78) from the *Z* stereoisomer of 77 and pyridylpyrrolinones (79) or pyrido[1,2-*a*](1,3)diazepines (80) from the *E* stereoisomer (Scheme 3). Experiments were carried out



SCHEME 3

¹³⁰ L. Vasvári-Debreczy, I. Hermecz, Z. Mészáros, P. Dvortsák, and G. Tóth, *J. C. S. Perkin I*, 227 (1980).

¹³¹ Z. Mészáros, J. Knoll, I. Hermecz, L. Vasvári-Debreczy, and Á. Horváth, Swiss Patent 605,940 [CA 90, 54970 (1979)].

¹³² Z. Mészáros, J. Knoll, I. Hermecz, L. Vasvári-Debreczy, P. Szentmiklósi, O. Simon, Á. Horváth, Á. Dávid, and G. Horváth, German Patent 2,315,422 [CA 80, 3560 (1974)].

¹³³ Z. Mészáros, I. Hermecz, L. Vasvári-Debreczy, Á. Horváth, Á. Dávid, G. Horváth, P. Dvortsák, M. Pongor-Csákvári, and V. Kovács-Mindler, *Mag. Kem. Lapja* 31, 281 (1976) [CA 86, 29677 (1977)].

¹³⁴ L. Vasvári-Debreczy, I. Hermecz, Z. Mészáros, Á. Horváth, and P. Simon-Párkányi, *J. C. S. Perkin I*, 795 (1978).

¹³⁵ L. Vasvári-Debreczy, I. Hermecz, and Z. Mészáros, to be published.

on the separated *E* and *Z* isomers of **77**, and it was demonstrated that fast *E*–*Z* isomerization takes place under the conditions of the ring closures.^{130,133–135}

In a phosphoryl chloride–polyphosphoric acid mixture the pyrido[1,2-*a*]-pyrimidines (**78**) were formed in high yield, as well as a small amount of the pyridylpyrrole derivatives (**83**) that were obtained from the pyridylpyrrolinones (**79**) through hydroxy to chloro exchange under the conditions of the ring closure. From the 6-methyl-substituted succinates (**77**: *R* = 6-Me) the pyrido[1,2-*a*]pyrimidines (**78**) and the pyridylpyrroles (**83**) were obtained in approximately equal amounts, in a good overall yield.^{132–134}

In Dowtherm A the pyrido[1,2-*a*]pyrimidines (**78**) and the pyridylpyrrolinones (**79**), contaminated with the double bond isomer (**82**), were obtained in good yield. The ratio of the products varied slightly with the substituents. From the 6-acetyl-amino-substituted succinate (**77**: *R* = 6-NHAc) the 1,8-naphthyridine (**81**: *R* = NHAc) was also obtained.¹³⁰

In ethanolic sodium ethoxide the pyrido[1,2-*a*]pyrimidines (**78**) and the pyridylpyrrolinones (**79**) were formed in an equilibrium reaction, the pyridylpyrrolinones being the preferred product. The pyrido[1,2-*a*]pyrimidines (**78**) were not obtained from the 6-substituted succinates (**77**: *R* = 6-OH, 6-Me, or 6-NHAc).¹³⁵

TABLE I
INFLUENCE OF REACTION CONDITIONS ON PRODUCT DISTRIBUTIONS
FROM PYRIDYL SUCCINATES **77**

R	Products (%)					
	POCl ₃ /PPA (110–120°C)		Dowtherm A (250°C)		NaOEt/NaOH (25°C, 15 min)	
	78	79 + 83	78	79 + 82	78	79 + 82
H	82	4	54	28	14	57
5-Me	83	4	50	32	11	55
6-Me	40	40	44	36	0	68

A comparison of the behavior of the *R* = H, 5-Me-, and 6-Me-substituted succinates (**77**) in the competitive cyclization reactions (Table I) revealed that in ethanolic sodium ethoxide at 25°C the 6-methyl group fully inhibited the ring closure onto the ring nitrogen. It also revealed that in phosphoryl chloride–polyphosphoric acid at 120°C the formation of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**78**: *R* = 6-Me) was only hindered, whereas at 250°C under the conditions of thermal ring closure, only a slight, if any, steric hindrance occurred. This suggests that the formation of the 6-substituted pyrido[1,2-*a*]-

pyrimidines (**71** and **74**) from the 6-substituted malonates (**70**) and acrylates (**73**), respectively, is not hindered under the conditions of thermal cyclization, and that the 1,8-naphthyridines (**72** and **76**) are formed not because pyrido[1,2-*a*]pyrimidine formation is hindered by the 6-substituent of the malonates (**70**) or acrylates (**73**), but because the 6-substituent of the first-formed pyrido[1,2-*a*]pyrimidines (**71** or **74**) sterically assists the subsequent pyrido[1,2-*a*]pyrimidine to 1,8-naphthyridine ring-transformation.¹³⁵

Ring closures of the 2-(2-pyridylaminomethylene)glutarates, homologs of **77**, yielded only 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, except for the thermal cyclization of the 6-acetamido derivative, in which the 1,8-naphthyridine was also obtained.^{130,132-135}

Cyclization of the malonates (**70**) and acrylates (**73**) has been carried out by the action of heat, in Dowtherm A,^{18,20,54,73,79,126,128,130,132,133,136-143} in diethylbenzene^{46,54,138,140} and in trichlorobenzene.¹⁴⁴ Cyclization has also occurred under acidic conditions in polyphosphoric acid,^{41,145-147} in phosphoryl chloride-polyphosphoric acid,^{73-79,132-134,148-151} in sulfuric acid-acetic anhydride¹⁵² and acetic acid-acetic anhydride mixtures,¹⁴⁶ and by the use of a basic reagent such as sodium ethoxide in ethanolic solution.¹³⁵

Shur and Israelstam⁴¹ presumed that the product (mp = 148-149°C) obtained by cyclization of the malonate (**70**; R = 6-Me) in polyphosphoric acid was the pyrido[1,2-*a*]pyrimidine (**71**; R = 6-Me). By preparing that compound in a polyphosphoric acid-phosphoryl chloride mixture; however,

¹³⁶ C. Gupta, A. Bhaduri, N. M. Khanna, and S. K. Mukherjee, *Indian J. Chem.* **9**, 201 (1971).

¹³⁷ J. K. Landquist, *J. Chem. Soc. C*, 2735 (1971).

¹³⁸ H. L. Yale, German Patent 2,318,821 [CA **80**, 14954 (1974)].

¹³⁹ M. Kac, F. Kovac, B. Stanovnik, and M. Tisler, *Gazz. Chim. Ital.* **105**, 1291 (1975).

¹⁴⁰ H. L. Yale, U.S. Patent 3,960,847 [CA **85**, 123965 (1976)].

¹⁴¹ J. P. Clayton, German Patent, 2,648,770 [CA **87**, 84987 (1977)]; Israeli Patent 50,797 [CA **94**, 103356 (1981)].

¹⁴² Sterling Drug Ins., British Patent 1,147,760 [CA **71**, 49967 (1969)].

¹⁴³ G. Y. Leshner, U.S. Patent 3,907,798 [CA **84**, 44130 (1976)].

¹⁴⁴ G. A. Reynolds, E. M. Robertson, and J. A. Van Allen, U.S. Patent 3,072,485 [CA **58**, 10903 (1963)].

¹⁴⁵ O. S. Wolfbeis and H. Junek, *Monatsh. Chem.* **110**, 1387 (1979).

¹⁴⁶ O. S. Wolfbeis, *Chem. Ber.* **110**, 2480 (1977).

¹⁴⁷ V. M. Neplyuev, T. A. Sinenko, and P. S. Pelkis, *Zh. Org. Khim.* **16**, 1483 (1980) [CA **94**, 3839 (1981)].

¹⁴⁸ G. Náray-Szabó, I. Hermecz, and Z. Mészáros, *J. C. S. Perkin I*, 1753 (1974).

¹⁴⁹ D. Bánfi, J. Volford, and Z. Mészáros, *J. Labelled Compd.* **11**, 409 (1975).

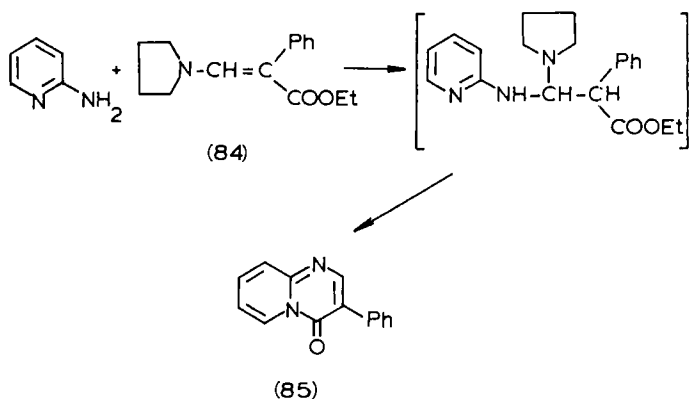
¹⁵⁰ I. Turcsán, I. Hermecz, S. Köszegi, I. Jellinek, J. Császár, and É. Somfai, HUNG. TELJES **13417** [CA **88**, 50910 (1978)].

¹⁵¹ I. Hermecz, Z. Mészáros, Á. Horváth, G. Nagy, S. Virág, P. Ritli, and L. Vasvári-Debrezy, HUNG. TELJES **17346** [CA **93**, 114,557 (1980)]; Austrian Patent 357,543 [CA **94**, 4039 (1981)].

¹⁵² M. E. Badic and J. P. Ambrus, Rumanian Patent 56,749 [CA **82**, 429 (1975)].

Mészáros *et al.*⁷⁵ found that it melts at 99–100°C. The structure was proved by UV, IR, and ¹H NMR. The product isolated by Shur and Israelstam was probably the monoester (mp = 153–154°C) of the malonate (**70**: R = 6-Me), which is easily formed from the pyridopyrimidine (**71**: R = 6-Me) under the conditions applied to the polyphosphoric acid reaction mixture.

By ring closure of the acrylates (**73**), 3-substituted 4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidines with chloroacetyl, 2-ethoxycarbonylvinyl, and nitro- and 4-chlorophenylsulfonyl substituents have been prepared.^{22,145–147} Reaction of 2-aminopyridine and the enamine (**84**) led to the 3-phenyl derivative (**85**), which is presumably formed by an addition–elimination mechanism.¹⁵³



Thermal cyclization of the isopropylidene ester of the malonates (**70**) was accompanied by decarboxylation at position 3, whereby 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**74**: R¹ = H) were obtained.^{79,142,143} When the cyclization was performed in phosphoryl chloride–polyphosphoric acid and the reaction mixture was treated with alcohol, 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid esters were isolated.¹⁵¹ Treatment of the reaction mixture with water gave carboxylic acids.

Besides the malonates (**70**), the monocyano (**86**: R = COOEt)^{29,87,154,155} and the dicyano derivatives (**86**: R = CN)^{156–159} were also subjected to

¹⁵³ A. Halleux and H. G. Viehe, *J. Chem. Soc. C*, 881 (1970).

¹⁵⁴ S. Nishigaki, M. Ishiba, K. Shinomura, and F. Yoneda, *J. Heterocycl. Chem.* **8**, 759 (1971).

¹⁵⁵ P. F. Juby, U.S. Patent 4,122,274 [*CA* **90**, 103998 (1979)].

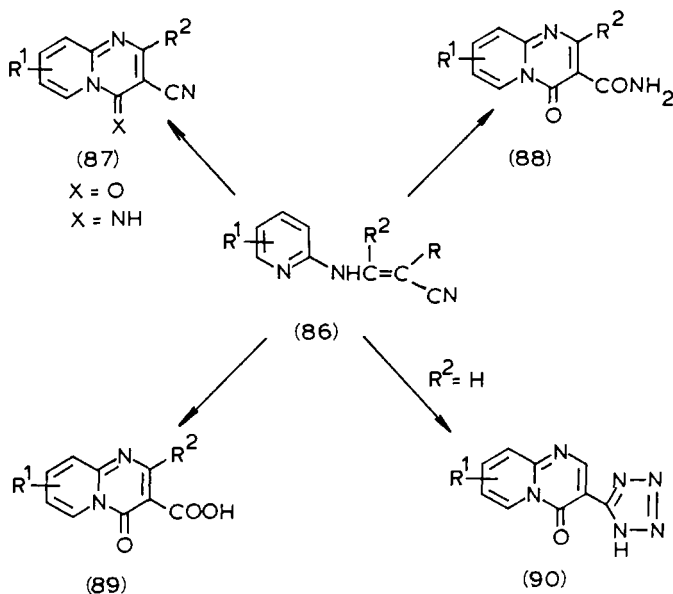
¹⁵⁶ Y. Okamoto, Y. Kurasawa, K. Tanagi, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* **22**, 243 (1974).

¹⁵⁷ J. Ceder and K. Vernmark, *Acta Chem. Scand., Ser. B* **B31**, 235 (1977).

¹⁵⁸ H. Junek and H. Schmidt, German Patent 2,519,816 [*CA* **86**, 43735 (1977)].

¹⁵⁹ H. Junek and H. Schmidt, *Monatsh. Chem.* **108**, 517 (1977).

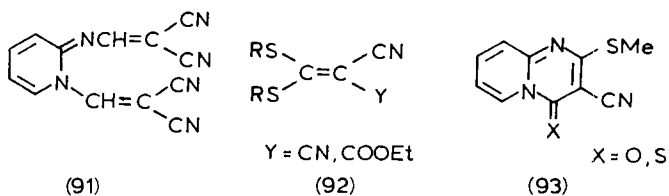
ring closure. The cyanoacetates (**86**: $R = \text{COOEt}$, $R^2 = \text{H}$) cyclized on vacuum distillation,²⁹ whereas the methyl derivatives ($R^2 = \text{Me}$) were heated⁸⁷ at 150°C to yield the 3-cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**87**: $X = \text{O}$). Cyclization in concentrated hydrochloric acid¹⁵⁴ gave the 3-carboxylic acids (**89**), whereas in tetrahydrofuran in the presence of sodium azide and aluminum chloride, the 3-tetrazolyl derivatives (**90**) were obtained.¹⁵⁵ Cyclization of the 6-methyl derivative (**86**: $R = \text{COOEt}$, $R^1 = 6\text{-Me}$, $R^2 = \text{H}$) did not occur in hot concentrated hydrochloric acid.¹⁵⁴



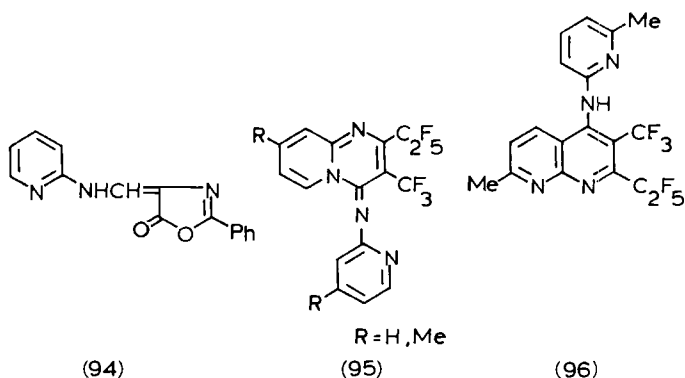
Products of 4-methylpyridine and ethoxymethylene cyanoacetate in various ring closure reactions were first described by Antaki,²⁹ but the correct structures (**86**: $R = \text{COOEt}$, $R^1 = 4\text{-Me}$, $R^2 = \text{H}$ and **87**: $R^1 = 8\text{-Me}$, $R^2 = \text{H}$, $X = \text{O}$) became apparent from the work of Nishigaki *et al.*¹⁵⁴ and Seidel.²⁸

Okamoto *et al.*¹⁵⁶ cyclized the dinitriles (**86**: $R = \text{CN}$, $R^2 = \text{H}$) by heating in 15% hydrochloric acid to obtain pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (**89**: $R^2 = \text{H}$). 2-Aminopyridinium chloride and ethoxymethylenemalononitrile at 110°C yielded 3-cyano-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine (**87**: $R^1 = R^2 = \text{H}$, $X = \text{NH}$) and compound **91**. Under similar conditions, 2-amino-3-methylpyridine gave a noncyclized product of type **91**.

For the product isolated from the reaction of 2-amino-6-methylpyridine and ethoxymethylenemalononitrile, Ceder and Vernmark¹⁵⁷ suggested structure **87** ($R^1 = 6\text{-Me}$, $R^2 = \text{H}$, $X = \text{NH}$). This proved to be incorrect,



however, after Okamoto *et al.*¹⁵⁶ reported that the same substances in ethanol produce **86** ($R = \text{CN}$, $R^1 = 6\text{-Me}$, $R^2 = \text{H}$), with a melting point and UV spectrum similar to those of Ceder and Vernmark's product. Junek and Schmidt^{158,159} studied the ring closure of the malononitriles (**86**: $R = \text{CN}$) in polyphosphoric acid at 110°C and in hot concentrated hydrochloric acid. In hot concentrated hydrochloric acid the $R^2 = \text{H}$ derivatives furnished the 3-carboxylic acids (**89**: $R^2 = \text{H}$), whereas those in which $R^2 \neq \text{H}$, gave the 3-nitriles (**87**: $X = \text{O}$). The 6-methyl derivatives (**86**: $R = \text{CN}$, $R^1 = 6\text{-Me}$) were cyclized in polyphosphoric acid and the products were described as 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids. In our opinion the products must be 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides (**88**: $R^1 = 6\text{-Me}$). Japanese workers¹⁶⁰ have also carried out the cyclization of the malononitrile (**86**: $R = \text{CN}$, $R^1 = 6\text{-Me}$, $R^2 = \text{H}$) in polyphosphoric acid and have concluded that the product was **88** ($R^1 = 6\text{-Me}$, $R^2 = \text{H}$). The melting points of the products obtained by both Schmidt and Junek and the Japanese authors agreed with that of the product prepared by Náray-Szabó *et al.*¹⁴⁸ from ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate with aqueous ammonia solution.



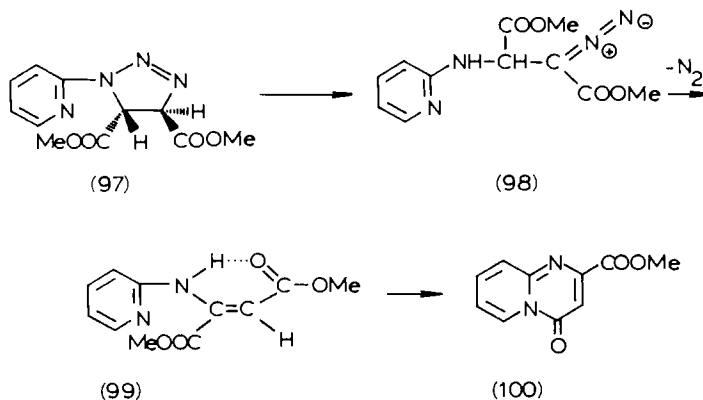
¹⁶⁰ H. Toyofuk and K. Tachibana, Japan Kokai 77/48,692 [*CA* **87**, 117895 (1977)].

Reaction of 2-aminopyridine and the ketene mercaptals (**92**) in the presence of sodium ethoxide gave the 2-methylthio derivatives (**93**).^{161,162} 2-Aminopyridine and 2-phenyl-4-ethoxymethylene-5-oxazole gave the condensation product **94**, which in the presence of sodium ethoxide at room temperature isomerized to 3-benzamido-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine.¹⁶³

4. Miscellaneous Syntheses

Flowers *et al.*¹⁶⁴ reacted perfluoro-2-methyl-2-pentene with 2-aminopyridine or 2-amino-4-methylpyridine in tetrahydrofuran at room temperature to obtain the pyrido[1,2-*a*]pyrimidines (**95**). Reaction with 2-amino-6-methylpyridine yielded the 1,8-naphthyridine (**96**).

Huisgen *et al.*¹⁶⁵ prepared the methyl pyrido[1,2-*a*]pyrimidine-2-carboxylate (**100**) from tetrazolo[5,1-*a*]pyridine and dimethyl maleate or fumarate at 160°C. The reaction presumably proceeds via the intermediates (**97–99**). Compound **100** was also obtained from 2-aminopyridine and dimethyl acetylenedicarboxylate.



On treatment with polyphosphoric acid, the pyridyltetrazole (**101**) furnished the 3-azido-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**102**) in 6% yield.¹⁶⁶

¹⁶¹ R. Gompper and W. Töpfl, *Chem. Ber.* **95**, 2871 (1962).

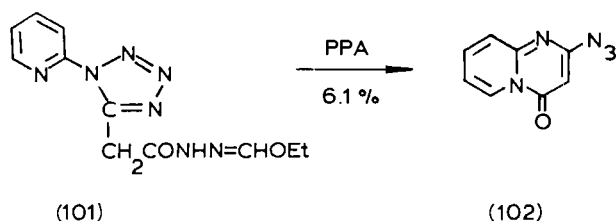
¹⁶² R. Gompper and W. Töpfl, German Patent 1,176,149 [*CA* **61**, 14689 (1964)].

¹⁶³ H. T. Clarke, J. R. Johnson, and R. Robinson, in "Chemistry of Penicillin" (J. W. Cornforth, ed.), pp. 757, 829; Princeton Univ. Press, Princeton, New Jersey, 1949.

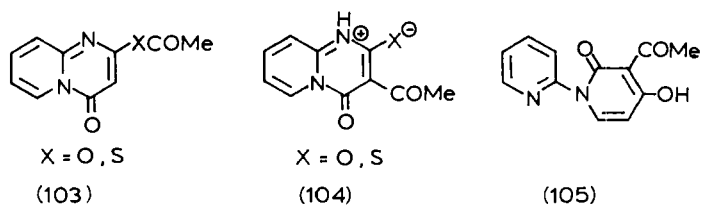
¹⁶⁴ W. T. Flowers, R. N. Haszeldine, A. Thomas, and C. R. Owen, *Chem. Commun.*, 487 (1974).

¹⁶⁵ R. Huisgen, K. Fraunberg, and H. J. Sturm, *Tetrahedron Lett.*, 2589 (1969).

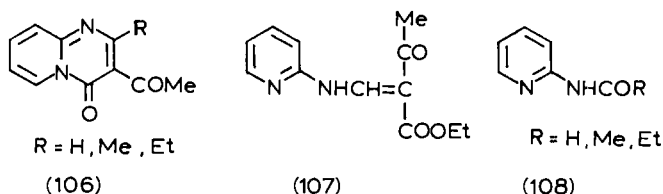
¹⁶⁶ M. Kovacic, S. Polanc, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.* **11**, 949 (1975).



By reacting ketene or diketene with 2-pyridylisocyanate or with isothiocyanate, Kato and Matsuda¹⁶⁷ obtained compounds **37** and **103–105**. They assumed that the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**37**, **103**, and **104**) are



formed in a 1,4-dipolar cycloaddition reaction. Kato and Matsuda¹⁶⁸ also reacted diketene with *N*-(2-pyridyl)imidates and with the Schiff bases obtained from 2-aminopyridine and benzaldehyde or acetophenone. The imidates gave the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**106**) in 38–97% yield.



Some 2-aminopyridine derivatives (**107** and **108**) were formed, also. Of the Schiff bases, only the benzaldehyde derivative reacted, yielding the 4-hydroxypyrido[1,2-*a*]pyrimidine (**109**), which was then oxidized with *o*-chloranil to the 4-oxo compound.

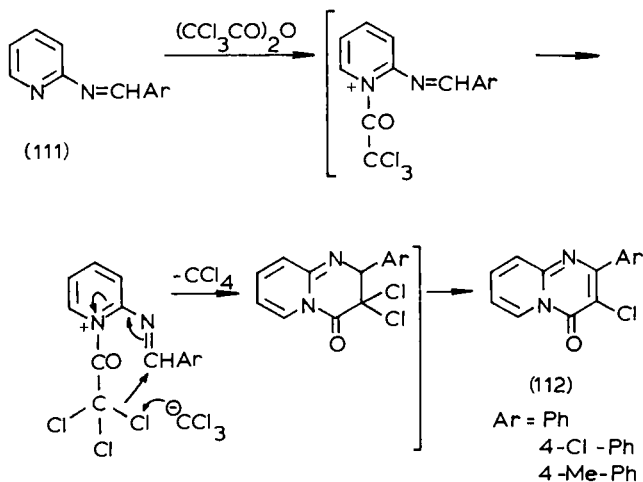


¹⁶⁷ T. Kato and S. Masuda, *Chem. Pharm. Bull.* **22**, 1542 (1974).

¹⁶⁸ T. Kato and S. Masuda, *Chem. Pharm. Bull.* **23**, 2251 (1975).

By reacting the formamidine (110) with diketene in benzene, Sakamoto *et al.*¹⁶⁹ isolated the pyrido[1,2-*a*]pyrimidine (106: R = H) in 10% yield.

According to Morimoto and Sekiya,^{170,171} in boiling toluene the Schiff bases (111) and trichloroacetic anhydride yield 2-aryl-3-chloro-4-oxo-pyrido[1,2-*a*]pyrimidines (112).



Yale and Spitzmiller⁹³ obtained 3-acetyl-2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines in 7–9% yield by treating 2-acetylacetamidopyridines with phosgene in benzene at room temperature.

Gilchrist *et al.*^{172–174} synthesized 2,3-diphenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (115) in good yield by reacting sulfimides (113) with cyclopropanones (114) at room temperature. Preparation of the oxo derivative (115: X = O) from 2-aminopyridine and methyl 2-phenylbenzoylacetate was unsuccessful.^{172,173}

Mesomeric betaines (116) and isocyanates gave rise to 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (117) in 36–64% yield.^{175–177}

¹⁶⁹ M. Sakamoto, K. Miyazawa, and Y. Tomimatsu, *Chem. Pharm. Bull.* **25**, 3360 (1977).

¹⁷⁰ T. Morimoto and M. Sekiya, *Hukusokan Kagaku Toronkai Koen Yoshishu*, 8th, 1975, 169 (1975) [*CA* **84**, 163799 (1976)].

¹⁷¹ T. Morimoto and M. Sekiya, *Chem. Pharm. Bull.* **25**, 1607 (1977).

¹⁷² T. L. Gilchrist, C. J. Harris, and C. W. Rees, *Chem. Commun.*, 487 (1974).

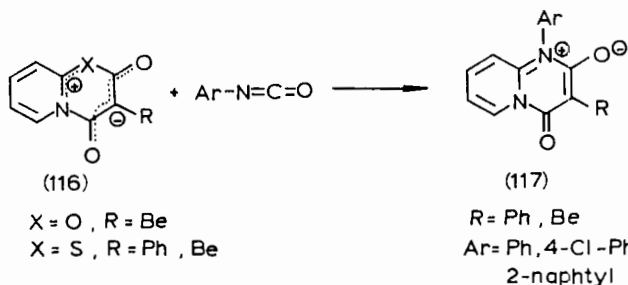
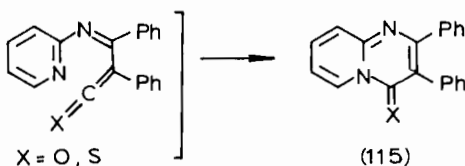
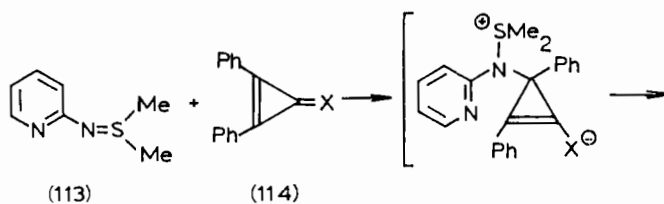
¹⁷³ T. L. Gilchrist, C. J. Harris, C. J. Moody, and C. W. Rees, *J. C. S. Perkin I*, 1969 (1975).

¹⁷⁴ T. L. Gilchrist and C. J. Moody, *Chem. Rev.* **77**, 409 (1977).

¹⁷⁵ T. Kappe and W. Golser, *Chem. Ber.* **109**, 3668 (1976).

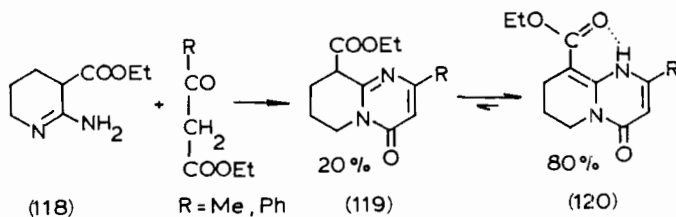
¹⁷⁶ W. Friedrichsen, E. Kujath, G. Liebezeit, R. Schmidt, and I. Schwarz, *Justus Liebig's Ann. Chem.*, 1655 (1978).

¹⁷⁷ T. Kappe, W. Golser, M. Hariri, and W. Stadlbauer, *Chem. Ber.* **112**, 1584 (1979).



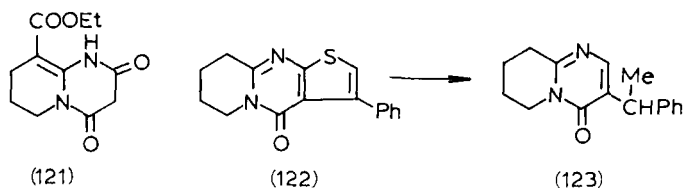
Syntheses starting from hydrogenated derivatives of 2-aminopyridines led to 4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidines.

By reacting 2-amino-3,4,5,6-tetrahydropyridine (118) with ethyl acetoacetate or ethyl benzoyl acetate in pyridine, Wamhoff and Lichtenthäler¹⁷⁸ obtained 1:4 equilibrium mixtures of the tautomers 119 and 120.



¹⁷⁸ H. Wamhoff and L. Lichtenthäler, *Chem. Ber.* **111**, 2813 (1978).

2-Amino-3,4,5,6-tetrahydropyridine and diethyl malonate in ethanolic sodium ethoxide yielded the 6,7,8,9-tetrahydro derivative of **63** ($R = H$)^{179,180} whereas the carbethoxy-substituted derivative (**118**) gave the pyrido[1,2-*a*]-pyrimidine (**121**).¹⁸¹

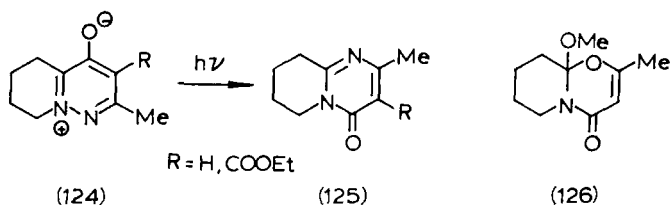


By refluxing valerolactim ether and aminomethylenemalononitrile in ethanol, Brown and Ienage¹⁸² prepared 3-cyano-4-imino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine.

Japanese researchers reacted valerolactim ethers with diethyl ethoxymethylenemalonate in the presence of ammonium acetate and obtained 6,7,8,9-tetrahydro derivatives of the ester (**71**: $R = H, 6\text{-Me}$).¹⁸³

Shvedov *et al.*¹⁸⁴ prepared the tetrahydropyrido[1,2-*a*]pyrimidine (**123**) by desulfuration of the tricyclic compound (**122**).

Yamazaki *et al.*¹⁸⁵ described the photolysis of the zwitterionic pyridazines (**124**) to tetrahydropyrido[1,2-*a*]pyrimidines (**125**).



Kato *et al.*¹⁸⁶ reported that the reaction of valerolactim ether and diketene gave rise to a pyrido[2,1-*b*](1,3)oxazine (**126**), which was converted with concentrated aqueous ammonia to the 6,7,8,9-tetrahydro derivative of **37**.

¹⁷⁹ J. Perronnet and A. Poittevin, German Patent 2,245,386 [CA 79, 78842 (1973)].

¹⁸⁰ J. Perronnet, A. Poittevin, and L. Taliani, French Demande 2,197,513 [CA 82, 11201 (1975)].

¹⁸¹ H. Wamhoff and L. Lichtenh ler, *Synthesis*, 426 (1975).

¹⁸² D. J. Brown and K. Ienage, *Aust. J. Chem.* **28**, 119 (1975).

¹⁸³ I. Agata, S. Noguchi, and K. Tanaka, Japan Kokai 73/34,897 [CA 79, 42537 (1973)].

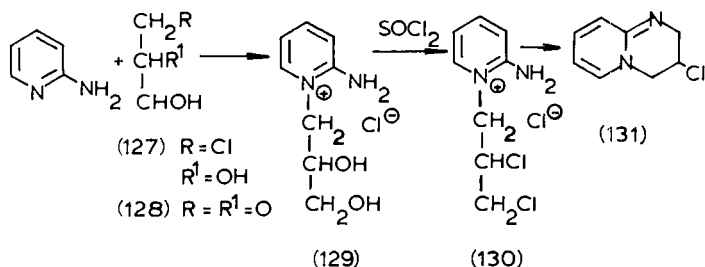
¹⁸⁴ V. I. Shvedov, I. A. Kharizomenova, and A. Grinyev, *Khim Geterotsikl. Soedin.*, 765 (1975) [CA 83, 164119 (1975)].

¹⁸⁵ T. Yamazaki, M. Nagata, S. Hirokami, and Miyakoshi, *Heterocycles* **8**, 377 (1977).

¹⁸⁶ T. Kato, Y. Yamamoto, and M. Kondo, *Heterocycles* **3**, 927 (1975).

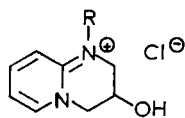
D. 3,4-DIHYDRO-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

By reacting 2-aminopyridine and epichlorohydrin, Knunjanz¹⁸⁷ obtained the hydrochloride of 3-hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine (**131**; R = OH). Analogous products from 4-methyl-, 5-methyl-, 5-halo- and 3,5-dibromo-substituted 2-aminopyridines have been prepared by Soviet workers.^{188,189} The same products arose from the reaction of 2-aminopyridines and 1,3-dichloro-2-propanol.^{188,189} Klusis and Kuthevicus¹⁹⁰ reacted 2-aminopyridine with 3-chloro-1,2-propanediol (**127**) or 2,3-



epoxypropanol (**128**). The resulting dihydroxy compound (**129**) was transformed with thionyl chloride to the dichloro compound (**130**), which was then cyclized with a base (aqueous silver oxide or sodium hydroxide) to the 3-chloro compound (**131**; R = Cl).

By the reaction of 2-(alkylamino or benzylamino)pyridines with epichlorohydrin or 1,3-dichloro-2-propanol, quaternary pyrido[1,2-*a*]pyrimidinium salts (**132**) were obtained.¹⁸⁸



R = alkyl, benzyl

(132)

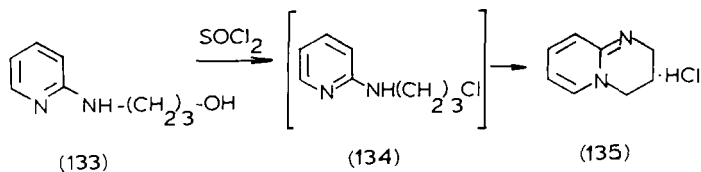
¹⁸⁷ I. L. Knunjanz, *Chem. Ber.* **68**, 397 (1935).

¹⁸⁸ V. Klusis and S. Kutkevicius, *Liet. TSR Aukst. Mokyklu Mokslo Darb., Chem. Chem. Technol.* **6**, 51 (1965) [*CA* **64**, 19607 (1966)].

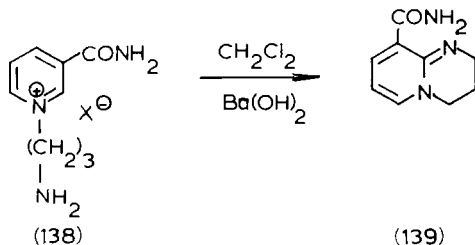
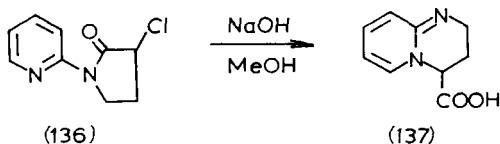
¹⁸⁹ J. Tamosiunas and V. Klusis, *Liet. TSR Aukst. Mokyklu Mokslo Darb., Chem. Chem. Technol.* **17**, 155 (1975) [*CA* **85**, 63026 (1976)].

¹⁹⁰ V. Klusis and S. Kutkevicius, *Liet. TSR Aukst. Mokyklu Mokslo Darb., Chem. Chem. Technol.* **7**, 67 (1965) [*CA* **64**, 19607 (1966)].

Sherlin and Velichkin¹⁹¹ reported that the reaction of 2-aminopyridine and 1-bromo-3-chloropropane afforded the 3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyrimidine (**135**) in 23% yield. Later Yamazaki *et al.*¹⁹² prepared the same product (**135**) from 2-chloropyridine and 3-aminopropanol via intermediates **133** and **134**.



Mandereau *et al.*¹⁹³ prepared the alcohol (**133**) by reducing ethyl 2-pyridylaminopropionate with lithium aluminum hydride. The alcohol was then transformed with thionyl chloride to the chloride (**134**) and cyclized with an equimolar amount of sodium hydroxide in methanol to the pyrido[1,2-*a*]pyrimidine (**135**). The 4-phenyl and 4-(*p*-tolyl) analogs were prepared in a similar fashion. The 4-(*p*-methoxyphenyl) derivative could only be obtained by heating the alcohol of type **133** in acetic anhydride. The pyrido[1,2-*a*]pyrimidine-4-carboxylic acid (**137**) was prepared by ring transformation of the pyridylpyrrolidinone (**136**) with methanolic sodium hydroxide.¹⁹³

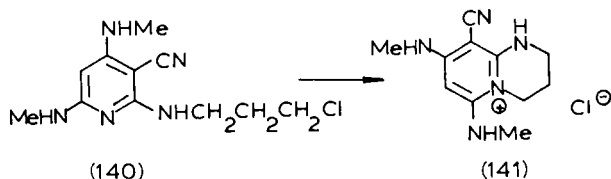


¹⁹¹ S. M. Sherlin and V. S. Velichkin, *J. Gen. Chem. USSR* **5**, 1586 (1935) [*CA* **30**, 2195 (1936)].

¹⁹² T. Yamazaki, M. Nagata, H. Araki, and F. Nohara, *J. Pharm. Soc. Jpn.* **88**, 216 (1968).

¹⁹³ J. Mandereau, E. Nguyen-Tri-Koung, and P. Reymaud, *Eur. J. Med. Chem.—Chim. Ther.* **9**, 344 (1974).

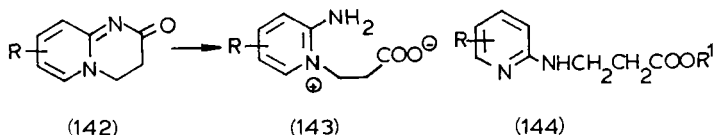
Gündel and Kramer¹⁹⁴ transformed the quaternary salt (138) derived from nicotinamide to 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine (139).



Bornatsch *et al.*¹⁹⁵ cyclized the pyridine derivative (140) to the pyrido-[1,2-*a*]pyrimidine (141) by heating in dimethylformamide with sodium iodide.

E. 2-Oxo-3,4-DIHYDRO-2*H*- AND 4-Oxo-2,3-DIHYDRO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

2-Oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines (142) and their hydrogen halide salts can be prepared by reacting 2-aminopyridine or methyl-substituted 2-aminopyridines with alkyl 3-halopropionates,^{20,196–200} 3-halopropionic acids,^{200–203} or alkyl acrylates^{18,20,197,204,205}



From the reaction of 3-iodopropionic acid and 2-aminopyridines, Krishnan obtained the pyridopyrimidines (142). From 2-amino-6-methyl-

¹⁹⁴ W. H. Gündel and W. Kramer, *Chem. Ber.* **111**, 2594 (1978).

¹⁹⁵ W. Bornatsch, H. Reel, and K. H. Schündehütte, *Chem. Ber.* **114**, 937 (1981).

¹⁹⁶ O. Yu. Magidson and A. S. Elina, *J. Gen. Chem. USSR* **16**, 1933 (1946) [*CA* **41**, 6220 (1947)].

¹⁹⁷ G. R. Lappin, *J. Org. Chem.* **23**, 1358 (1958).

¹⁹⁸ Y. Okamoto, T. Kato, A. Takeda, T. Ueda, and T. Tsuji, *Chem. Pharm. Bull.* **18**, 1064 (1970).

¹⁹⁹ Y. Okamoto, A. Takeda, and T. Ueda, *Chem. Pharm. Bull.* **19**, 764 (1971).

²⁰⁰ R. Adams and I. J. Pachter, *J. Am. Chem. Soc.* **74**, 4906 (1952).

²⁰¹ M. Krishnan, *Proc. Indian Acad. Sci. Sect. A* **42A**, 289 (1955) [*CA* **50**, 5679 (1956)].

²⁰² M. Melandri, A. Buttini, and G. DeGiuli, *Boll. Chim. Farm.* **103**, 895 (1964) [*CA* **62**, 10435 (1965)].

²⁰³ A. Kirpal and B. Wojnar, *Chem. Ber.* **71**, 1261 (1938).

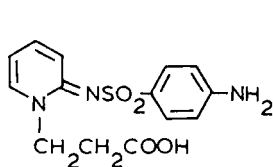
²⁰⁴ R. Baltrusis, A. Maciulis, and A. Purenas, *Liet. TSR Mokslu Acad. Darb. Ser. B*, 125 (1962) [*CA* **58**, 6827 (1963)].

²⁰⁵ R. Baltrusis and Z. Beresnevicius, *Khim. Geterotsikl. Soedin.*, 215 (1971) [*CA* **75**, 48846 (1971)].

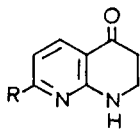
pyridine the pyridopyrimidine (**142**: R = 6-Me) was formed in low yield, and an additional product was isolated that was not identified.²⁰¹

Lappin^{20,197} reported that the reaction of 2-aminopyridines with alkyl 3-chloropropionates to give the pyrido[1,2-*a*]pyrimidines (**142**) is accompanied by the dehydrohalogenation of the propionates. In the case of 2-amino-6-methylpyridine this side reaction becomes exclusive. From alkyl acrylates and 2-aminopyridine or its 4- and 5-methyl derivatives, Lappin obtained a mixture of the pyrido[1,2-*a*]pyrimidines (**142**: R = H, 7-Me, 8-Me) and the 2-pyridylaminopropionates (**144**). In reactions lasting only 2 to 3 hours the pyrido[1,2-*a*]pyrimidines were mainly formed, whereas in prolonged reactions (20–100 hours) the propionates were the main products. 2-Amino-3-methylpyridine gave only the pyrido[1,2-*a*]pyrimidine (**142**: R = 9-Me), whereas from 2-amino-6-methylpyridine only the propionate (**144**: R = 6-Me) was obtained.

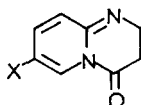
2-Oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines (**142**) may easily be converted (e.g., by heating in water) to the betaines (**143**)^{200,204} The latter can also be prepared from 2-aminopyridines with propiolactone,²⁰⁶ acrylic acid,¹⁸ 3-substituted propionitriles, and other acrylic acid derivatives.^{207,208} The betaines (**143**) revert to the bicyclic compounds (**142**) upon heating in acid.^{200,204,206,207}



(145)



(146)



(147)

Pyrido[1,2-*a*]pyrimidine (**142**: R = H) was also prepared from the pyridine derivative (**145**) by heating in concentrated hydrochloric acid.¹⁹⁶

Adams and Pachter¹⁸ synthesized the 3-hydroxy derivative of (**142**: R = H) by reacting 2-aminopyridine and 3-bromo-2-hydroxypropionic acid in in chloroform and also by heating the appropriate hydroxy derivative of the betaine (**143**) in concentrated hydrobromic acid. The authors then amended their earlier conclusions,²⁰⁹ in which incorrect structures were assigned to the betaine and to the pyrido[1,2-*a*]pyrimidine.

²⁰⁶ C. O. Hurd and S. Hayao, *J. Am. Chem. Soc.* **77**, 117 (1955).

²⁰⁷ P. Buckus, G. Dienys, and N. Ragoutiene, *Zh. Obshch. Khim.* **33**, 1236 (1963) [*CA* **59**, 10036 (1963)].

²⁰⁸ P. Buckus, N. Ragoutiene, and A. Buckiene, *Zh. Obshch. Khim.* **34**, 3847 (1964) [*CA* **62**, 9128 (1965)].

²⁰⁹ R. Adams and V. V. Jones, *J. Am. Chem. Soc.* **71**, 3826 (1949).

The 3-methyl derivative of (**142**: R = H) was prepared by Krishnan²¹⁰ from 2-aminopyridine and methyl methacrylate or methyl 3-bromoisobutyrate. These reagents, however, were not able to transform the methyl derivatives of 2-aminopyridine to pyrido[1,2-*a*]pyrimidines.²⁰⁹ Reaction of 2-aminopyridine with ethyl 3-bromobutyrate and ethyl crotonate also was not successful.

Da Settimo *et al.* found that 6-substituted 2-pyridylaminopropionic acid in polyphosphoric acid^{211–214} or sulfuric acid²¹¹ gives rise to 1,8-naphthyridines (**146**) and not to 6-substituted 4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines.

Okamoto *et al.* prepared the pyrido[1,2-*a*]pyrimidines (**142**: R = H, Me) by heating 2-aminopyridines with ethyl 3-chloropropionimidate hydrochloride in ethanol or acetonitrile. In the case of 2-aminopyridine and 2-amino-4-methylpyridine, not only **142** (R = H, 8-Me) but also the 2-imino derivatives were isolated, which on treatment with acid were transformed to 2-oxopyrido[1,2-*a*]pyrimidines (**142**). With 2-amino-6-methylpyridine or 2-aminoquinoline, only dehydrogenation of the starting imidate was observed.^{198,199}

Adams and Pachter²⁰⁰ pointed out that, in contradiction to the report of Kirpal and Wojnar,²⁰³ the product obtained from 2-aminopyridine and 3-chloropropionic acid in hydrochloric acid was not the betaine (**143**: R = H) but the pyrido[1,2-*a*]pyrimidine (**142**: R = H).

2-Amino-5-halopyridines displayed different behavior. According to Hurd and Hayao,²⁰⁶ with propiolactone in acetone, 2-amino-5-bromopyridine gives the betaine (**143**: R = 5-Br), whereas with 3-bromopropionic acid at 100°C without solvent, the hydrobromide of 4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine (**147**: X = Br) is formed.

Baltrusis and Beresnevicius²⁰⁵ found that a mixture of 2-amino-5-chloropyridine and methyl acrylate in acetic acid in a sealed tube at 100°C gives 4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine (**147**: X = Cl) and the propionic acid (**144**: R = 5-Cl, R¹ = H), but at room temperature the mixture instead gives 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine (**142**: R = 7-Cl) and the propionate (**144**: R = 5-Cl, R¹ = Me). Compound (**147**: X = Cl)

²¹⁰ M. Krishnan, *Proc. Indian Acad. Sci., Sect. A* **49A**, 31 (1959) [*CA* **53**, 18050 (1959)].

²¹¹ S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I. Tonetti, *Farmaco, Ed. Sci.* **30**, 237 (1975).

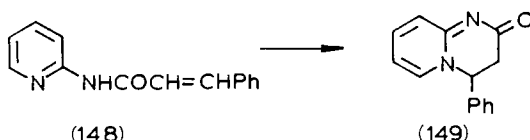
²¹² A. Da Settimo, G. Primofiore, G. Biagi, and V. Santerini, *Farmaco, Ed. Sci.* **31**, 587 (1976).

²¹³ A. Da Settimo, G. Biagi, G. Primofiore, P. L. Ferrarini, and O. Livi, *Farmaco, Ed. Sci.* **33**, 770 (1978).

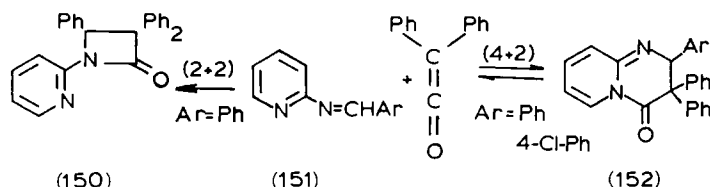
²¹⁴ A. Da Settimo, G. Biagi, G. Primofiore, P. L. Ferrarini, and O. Livi, *J. Heterocycl. Chem.* **17**, 1225 (1980).

could be hydrolyzed to the propionic acid (**144**: R = 5-Cl, R¹ = H), and the 2-oxo isomer (**142**: R = 7-Cl) to the betaine (**143**: R = 5-Cl). Under both of the above conditions 2-amino-5-bromopyridine and methyl acrylate yielded only noncyclized products, whereas upon standing for 1 month in acetic anhydride, the 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine (**142**: R = 7-Br) was obtained.

From 2-aminopyridine and cinnamoyl chloride Tkachenko *et al.*²⁵ prepared the amide (**148**) and transformed it to 2-oxopyrido[1,2-*a*]pyrimidine (**149**) by heating in ethanol.



Boedeker and Courault²¹⁵ reacted Schiff bases (**151**) derived from 2-aminopyridine and aromatic aldehydes with diphenylketene. In benzene at room temperature 4-oxopyrido[1,2-*a*]pyrimidines (**152**) were obtained in a reversible [4 + 2] cycloaddition reaction, whereas upon boiling mesitylene, irreversible [2 + 2] cycloaddition yielded azetidinones (**150**). Previously Sakamoto *et al.*²¹⁶ prepared the azetidinones (**150**) in boiling xylene.



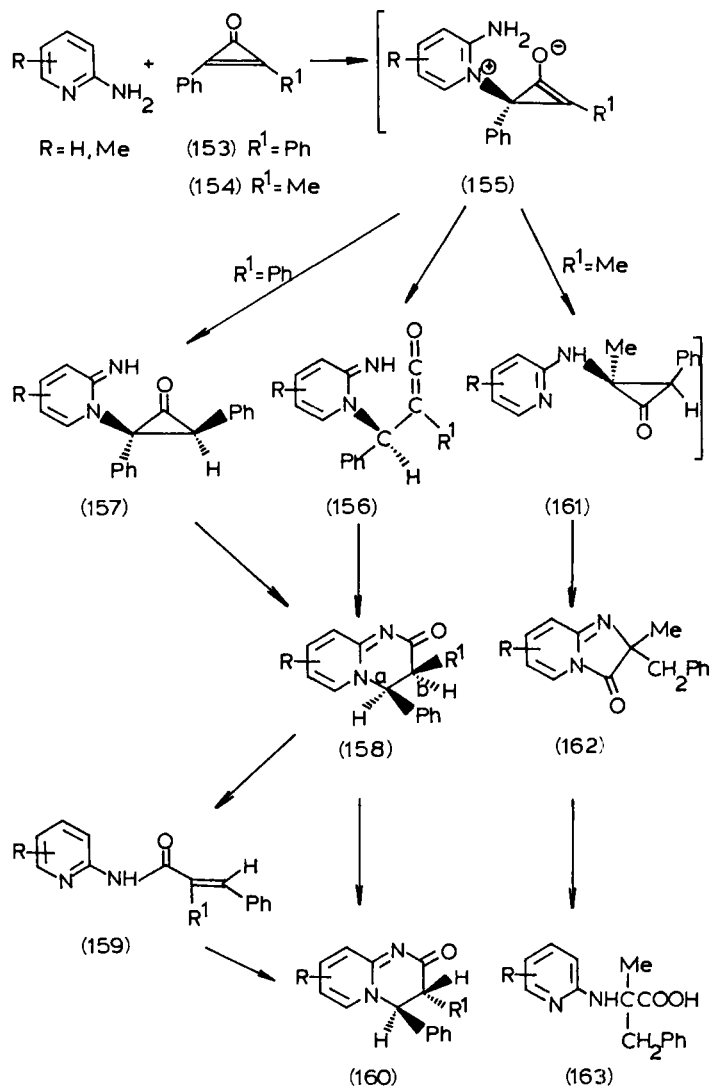
Kascheres *et al.*^{217,218} investigated the reaction of 2-aminopyridines with diphenylcyclopropenone (**153**) and methylphenylcyclopropenone (**154**). 2-Aminopyridines and diphenylcyclopropenone (**153**) in ether gave rise to *cis*-2-oxopyrido[1,2-*a*]pyrimidine (**158**: R¹ = Ph) and the amide (**159**: R¹ = Ph). In methanol in 1 to 2 days both *cis*- and *trans*-2-oxopyrido[1,2-*a*]pyrimidines (**158**: R¹ = Ph and **160**: R¹ = Ph) and the amide (**159**: R¹ = Ph) were formed, whereas on prolonged standing (5–24 days), only

²¹⁵ J. Boedeker and K. Courault, *Tetrahedron* **34**, 101 (1978).

²¹⁶ M. Sakamoto, K. Miyazawa, and Y. Tomimatsu, *Chem. Pharm. Bull.* **24**, 2532 (1976).

²¹⁷ A. Kascheres and J. A. R. Rodriques, *J. Org. Chem.* **40**, 1440 (1975).

²¹⁸ A. Kascheres, J. A. R. Rodriques, and A. R. A. Santana, *J. Org. Chem.* **41**, 3546 (1976).



SCHEME 4

the trans product and the amide were obtained. The cis compound (**158**; R¹ = Ph) was unstable in solution and underwent transformation in chloroform to the amide (**159**; R¹ = Ph) and in methanol to the trans isomer (**160**; R¹ = Ph) and the amide (**159**; R¹ = Ph). Finally, the amide (**159**; R¹ = Ph, R = 4-Me or 3-Me) in methanol slowly cyclized to the trans compound (**160**; R¹ = Ph, R = 8-Me and 9-Me, respectively) but not the cis

stereoisomer (**158**). These observations permitted the conclusion that in the reaction of 2-aminopyridine and **153**, the *cis*-2-oxopyrido[1,2-*a*]pyrimidines (**158**: $R^1 = \text{Ph}$) are the primary products. Furthermore, because the amount of the *trans* compound (**160**: $R^1 = \text{Ph}$) obtained from the amides (**159**) does not account for the amount of **160** obtained under similar conditions in the reaction of 2-amino-pyridine and **153**, the *trans*-2-oxopyrido[1,2-*a*]pyrimidine must be formed in part directly from the *cis* isomer, via enolization of the oxo group.

The relative instability of the *cis*-2-oxopyrido[1,2-*a*]pyrimidines (**158**: $R^1 = \text{Ph}$) was explained by the steric conditions of the molecule: the anti-periplanar arrangement of bonds "a" and "b" facilitates a concerted olefin-forming elimination reaction leading to the amide (**159**: $R^1 = \text{Ph}$). The reaction is also aided by the unfavorable interactions arising among the *cis*-4-phenyl groups and between the 4-phenyl group and the 6-H atom.

From 2-amino-6-methylpyridine and **153**, only the amide (**159**: $R^1 = \text{Ph}$, $R = 6\text{-Me}$) was formed.

Reactions with methylphenylcyclopropanone (**154**) provided an opportunity to compare the reactivities of the two different C—CO bonds. The reaction of 2-aminopyridines with methylphenylcyclopropanone (**154**) proceeded more slowly than with the diphenyl analog (**153**). In ether, formation of the *cis*-2-oxopyrido[1,2-*a*]pyrimidines (**158**: $R^1 = \text{Me}$) and/or the imidazo[1,2-*a*]pyridines (**162**) was observed, indicating that the cycloaddition proceeds via cleavage of the PhC—CO bond. The methyl-substituted *trans*-2-oxopyrido[1,2-*a*]pyrimidine (**160**: $R^1 = \text{Me}$) was only detected in the reaction mixture of 2-amino-3-methylpyridine, where the ^1H NMR spectrum exhibited signals assigned to **160** ($R^1 = \text{Me}$, $R = 9\text{-Me}$). The compound was not isolated. The imidazo[1,2-*a*]pyridines (**162**) readily hydrolyzed to the acids (**163**), work-up therefore leading mainly to isolation of the acids.

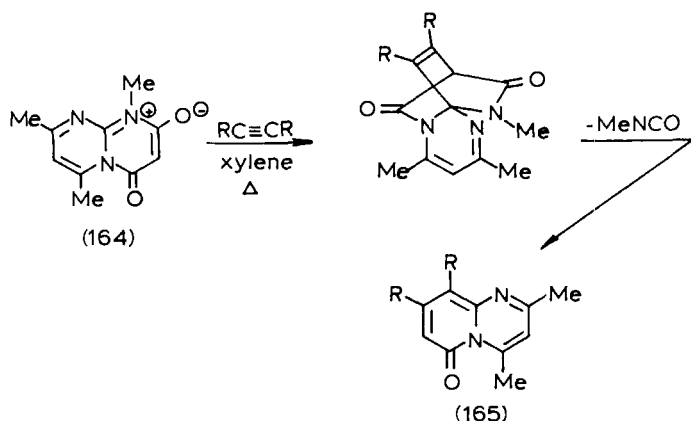
From 2-amino-6-methylpyridine only the imidazo [1,2-*a*]pyridine (**162**: $R = 5\text{-Me}$) was formed; this was interpreted in terms of the steric effect of the 6-methyl group.

In the course of mechanistic studies it was established that aniline does not react with the cyclopropanones (**153** and **154**) even under reflux conditions. It was therefore assumed that the formation of (**158**) involves initial nucleophilic attack by the aminopyridine ring nitrogen on the electrophilic cyclopropanone ring. In this way **155** is formed, which is then transformed via the reactive intermediates (**156**, **157**, and/or **161**) to the products. Kascheres *et al.* noted that the formation of **157** is formally a stereospecific *trans* addition of the 2-aminopyridines to the double bond of the cyclopropanone (**153**). Such stereospecificity has been observed in kinetically controlled Michael additions.

F. MISCELLANEOUS PYRIDO[1,2-*a*]PYRIMIDINES

In this section the preparation of 6-oxopyrido[1,2-*a*]pyrimidines and syntheses of hexahydro- and perhydropyrido[1,2-*a*]pyrimidines are reviewed.

Potts and Hsia²¹⁹ prepared unsaturated 6-oxo-6*H*-pyrido[1,2-*a*]pyrimidines (**165**) by the 1,4-dipolar cycloaddition of dipolarophilic acetylene derivatives to pyrimido[1,2-*a*]pyrimidine betaines (**164**).



Kubo *et al.*^{220–222} obtained 6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidines (**172**) by reacting 1,3-diaminopropane or its *N*-methyl derivative with either the pyridone (**167**) or the ester (**166**).

The reaction with pyridone (**167**) was interpreted as proceeding by the formation of the pyridone (**168**), followed by the Smiles rearrangement leading to the spiro compound (**169**), which by ring opening provides the pyrimidine derivative (**170**). In a subsequent cyclization step the pyrido[1,2-*a*]pyrimidine skeleton (**171**) is formed, and finally hydrolysis of the imino group leads to the 6-oxo derivative (**172**). In the homologous imidazo[1,2-*a*]pyridine series, the 5-iminoimidazo[1,2-*a*]pyridine intermediate of type (**171**) could be isolated.

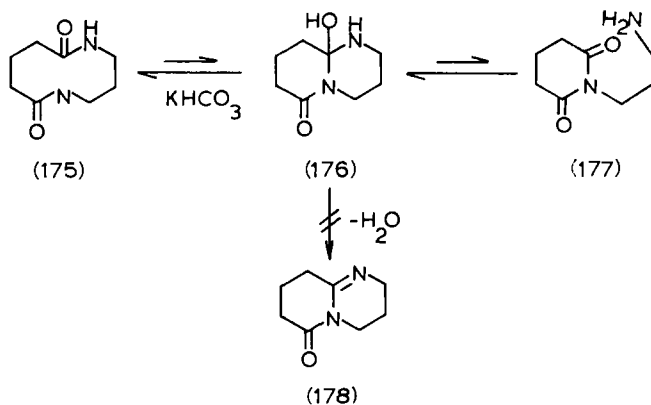
²¹⁹ K. T. Potts and R. K. C. Hsia, *J. Org. Chem.* **38**, 3485 (1973).

²²⁰ K. Kubo, N. Ito, I. Sozu, Y. Isomura, H. Homma, and M. Kurakami, German Patent 2,731,982 [*CA* **88**, 136596 (1978)]; British Patent 1,588,166 [*CA* **96**, 68987 (1982)].

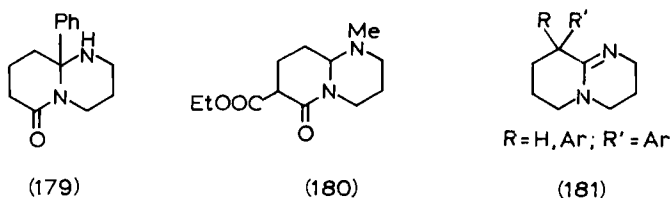
²²¹ K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, and M. Murakami, *Chem. Pharm. Bull.* **27**, 1207 (1979).

²²² K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, and M. Murakami, *J. Pharm. Soc. Jpn.* **99**, 880 (1979).

Dale and Coulon²²⁵ reported that heating glutaric acid and 1,3-diaminopropane at 200°C followed by vacuum distillation yielded 6-oxo-2,3,4,7,8,9-hexahydro-6*H*-pyrido[1,2-*a*]pyrimidine (**178**). The piperidine ring homologs of **178** could not be prepared in a similar fashion. Attempts to prepare the pyrido[1,2-*a*]pyrimidine (**178**) by heating the macrocyclic compound (**175**) in toluene or xylene in the presence of methanesulfonic acid remained unsuccessful.²²⁶



Glover and Rapoport²²⁷ have shown that pH-dependent equilibration of **175** and **177** proceeds via the pyrido[1,2-*a*]pyrimidine (**176**).



6-Oxopyrido[1,2-*a*]pyrimidines (**179**) were obtained by heating 4-benzoylbutanoic acid and 1,3-diaminopropane without solvent²²⁸ at 150–160°C or by boiling xylene in the presence of *p*-toluenesulfonic acid.^{229–232} From

²²⁵ J. Dale and R. Coulon, *J. Chem. Soc.*, 3487 (1965).

²²⁶ H. Gringerg, S. Lamdan, and C. H. Gaozza, *J. Heterocycl. Chem.* **12**, 763 (1975).

²²⁷ G. I. Glover and H. Rapoport, *J. Am. Chem. Soc.* **86**, 3397 (1964).

²²⁸ J. R. Geigy A.-G., Belgian Patent 659,530 [*CA* **64**, 6665 (1966)].

²²⁹ W. J. Houlihan, U.S. Patent 3,334,099 [*CA* **69**, 96769 (1968)].

²³⁰ P. Aeberli and W. J. Houlihan, *J. Org. Chem.* **34**, 165 (1969).

²³¹ W. J. Houlihan, U.S. Patent 3,454,585 [*CA* **71**, 61387 (1969)].

²³² W. J. Houlihan, U.S. Patent 3,526,626 [*CA* **73**, 98976 (1970)].

appropriate starting materials the 8,8-dimethyl derivative of **179** could also be prepared.²²⁸

Wollweber *et al*²³³ prepared the perhydropyridopyrimidine (**180**) from *N*-methyl-1,3-diaminopropane and 4,4-diethoxycarbonylbutylaldehyde.

On heating above 150°C, 4-halo-2-substituted valeronitriles and 1,3-diaminopropane yielded the 9-substituted pyrido[1,2-*a*]pyrimidines (**181**).^{234,235}

Langdale-Smith²³⁶ reacted an aqueous solution of glutaraldehyde with *N*-methyl-1,3-diaminopropane in the presence of potassium cyanide and obtained 1-methyl-6-cyanoperhydropyrido[1,2-*a*]pyrimidines.

Ricart *et al.*^{237,238} reported that hydrogenation of 1-[*N*-(5-hydroxypentyl)-3-aminopropyl]aziridine over Raney nickel gave a mixture of the unsubstituted and the 1-ethyl-substituted perhydropyrido[1,2-*a*]pyrimidine. The former was also obtained by reacting 5-hydroxypentylamine and acrylonitrile, followed by hydrogenation over Raney nickel.

Modeling the biological oxidation of tertiary amines, Audeh and Lindsay-Smith²³⁹ prepared perhydropyrido[1,2-*a*]pyrimidine by the oxidative cyclization of 3-piperidino propylamine by use of potassium hexacyanoferrate(III) in potassium hydroxide solution.

Möhrle and Mayer^{240,241} oxidized the 3-piperidinopropylamine (**182**) with mercuric acetate-EDTA reagent to obtain the pyrido[1,2-*a*]pyrimidine (**184**). Oxidation of the *N*-monomethyl and *N,N*-dimethyl derivatives of **182** resulted in the *N*-methyl and *N,N*-dimethylpiperidone derivatives of **185**.²⁴¹ If the reactions were carried out without the addition of EDTA, the perhydropyrido[1,2-*a*]pyrimidine(**183**) and its *N*-methyl derivative also could be isolated from the reaction mixture.²⁴¹ The pyrido[1,2-*a*]pyrimidine (**184**) was also prepared from the piperidone (**186**).²⁴² The oxidative cyclization was successfully when applied to the piperidinopropionamides (**187**) to prepare the pyrido[1,2-*a*]pyrimidines (**188**) in addition to 2-oxopiperidinopropionamides.²⁴³

²³³ H. Wollweber, J. Kurz, and W. Nägele, *Arch. Pharm. (Weinheim. Ger.)* **304**, 774 (1971).

²³⁴ G. Schmidt, German Patent 1,171,928 [*CA* **61**, 5664 (1964)].

²³⁵ F. Ishikawa, T. Imano, and Y. Abiko, Japan Kokai Tokkyo Koho 78/78,889 [*CA* **90**, 23052 (1979)].

²³⁶ R. A. Langdale-Smith, *J. Org. Chem.* **36**, 226 (1971).

²³⁷ G. Ricart, D. Couturier, and C. Glacet, *C. R. Hebd. Seances Acad. Sci., Ser. C* **280**, 953 (1975).

²³⁸ G. Ricart and D. Couturier, *Rev. Roum. Chim.* **25**, 541 (1980) [*CA* **94**, 139069 (1981)].

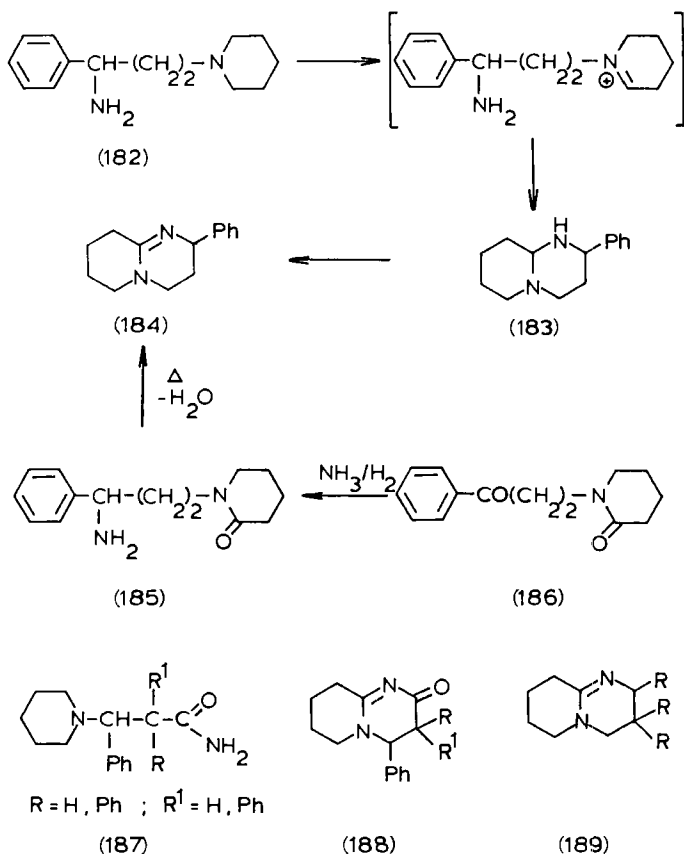
²³⁹ C. A. Audeh and J. R. Lindsay-Smith, *J. Chem. Soc., B*, 1745 (1971).

²⁴⁰ H. Möhrle and S. Mayer, *Tetrahedron Lett.*, 5173 (1967).

²⁴¹ H. Möhrle and S. Mayer, *Arch. Pharm. (Weinheim. Ger.)* **306**, 209 (1973).

²⁴² H. Möhrle and R. Engelsing, *Arch. Pharm. (Weinheim. Ger.)* **306**, 325 (1972).

²⁴³ H. Möhrle and H. J. Hemmerling, *Arch. Pharm. (Weinheim. Ger.)* **310**, 200 (1977).



Beck *et al.*²⁴⁴ reported chlorination of 3-piperidinopropionitrile leading to the pyrido[1,2-*a*]pyrimidine (**189**; $R = Cl$).

A three-step synthesis of 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine (**189**; $R = H$) starting from piperidone and acrylonitrile has also been reported.^{245,246}

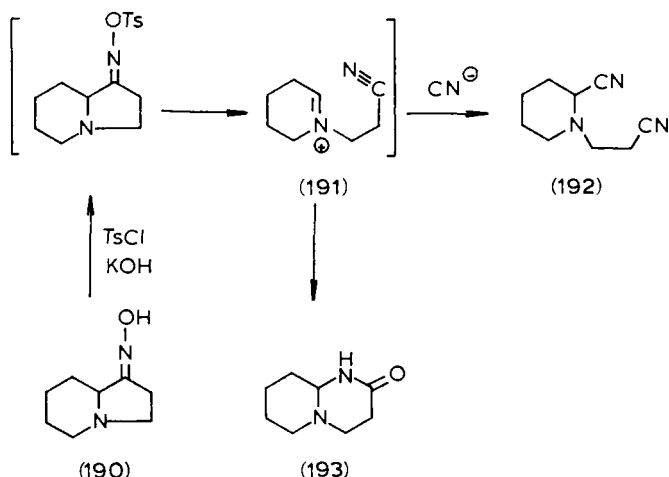
Beckmann rearrangement of the oxime tosylate (**190**) to provide the 2-oxoperhydropyrido[1,2-*a*]pyrimidine (**193**) was reported by Grob *et al.*²⁴⁷

²⁴⁴ G. Beck, H. Heitzer, and H. Holtschmidt, *Angew. Chem.* **86**, 134 (1974).

²⁴⁵ Farbenfabriken Bayer A.-G., French Patent 1,491,791 [*CA* **69**, 67412 (1968)].

²⁴⁶ J. Rokach, P. Hamel, N. R. Junter, G. Reader, C. S. Rooney, P. S. Anderson, E. J. Cragoe, Jr., and L. R. Mandel, *J. Med. Chem.* **22**, 237 (1979).

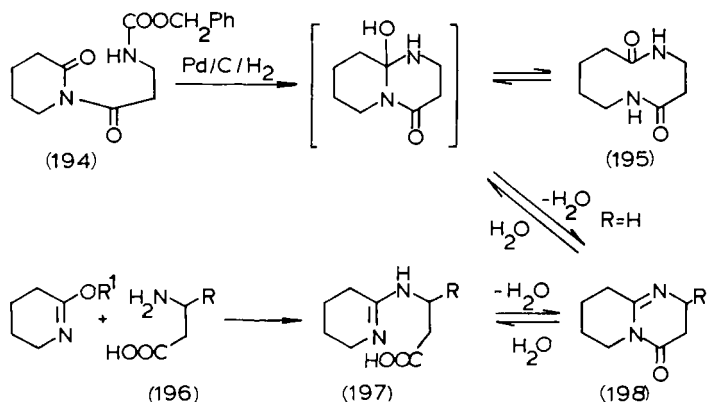
²⁴⁷ C. A. Grob, H. P. Fischer, H. Link, and E. Renk, *Helv. Chim. Acta* **46**, 1190 (1963).



In the presence of cyanide ion the intermediate (191) afforded the dinitrile (192) instead of 193.

Profft and Becker²⁴⁸ prepared 4-oxopyrido[1,2-*a*]pyrimidines (198: R = H, Ph) by reacting δ -valerolactim ethers with 3-aminopropionic acids (196: R = H, Ph).

Shemyakin and co-workers^{249,250} transformed the dipeptide (195), prepared by catalytic hydrogenation of the piperidone (194), to the 4-oxo-



²⁴⁸ E. Profft and F. J. Becker, *J. Prakt. Chem.* **30**, 18 (1965).

²⁴⁹ V. K. Antonov, Z. E. Agadzhanian, T. R. Telesnina, and M. N. Shemyakin, *Zh. Obshch. Khim.* **35**, 2231 (1965) [*CA* **64**, 11310 (1966)].

²⁵⁰ M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, V. I. Shchelokov, and Z. E. Agadzhanian, *Tetrahedron* **21**, 3537 (1965).

4*H*-pyrido[1,2-*a*]pyrimidine (**198**; R = H) by heating in xylene. Formation of **198** (R = H) from the dipeptide (**195**) was also detected by a mass spectrometer.²⁵¹

III. Reactions of Pyrido[1,2-*a*]pyrimidines

Within the following subsections the stability of the bicyclic ring system, plus the hydrogenation, reduction, dehydrogenation, oxidation, and quaternization of the compounds are reviewed. This is followed by discussion of substitution reactions affecting the pyrido[1,2-*a*]pyrimidine ring, transformations of the side chains, and finally ring transformation reactions.

A. PYRIDO[1,2-*a*]PYRIMIDINIUM SALTS

In spite of their aromatic character, the pyrido[1,2-*a*]pyrimidinium salts are readily converted by alkalis to the enamines (**5**). Under acidic conditions the enamines (**5**) easily revert to the pyrido[1,2-*a*]pyrimidinium salts.^{5,6,9} The pyrido[1,2-*a*]pyrimidinium salts do not suffer hydrolysis upon heating in hydrochloric acid.³

Tamura and Ono demonstrated by UV and ¹H-NMR spectroscopy that in ethanolic solution or in deuteromethanol in the presence of triethylamine, the pyrido[1,2-*a*]pyrimidinium chloride (**16**) is transformed to a 4-alkoxy-4*H*-pyrido[1,2-*a*]pyrimidine. The reaction is reversible.⁹

On treatment of a solution of the pyrido[1,2-*a*]pyrimidinium salt (**16**) with potassium permanganate in 2 *N* sulfuric acid, 11% 2-aminopyridine, 1% 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine, and traces of 2-nitropyridine were isolated from the reaction mixture.⁹ When 2,4-dimethylpyrido[1,2-*a*]pyrimidinium iodide was oxidized with aqueous potassium permanganate at 50–60°C, 2-acetamidopyridine was obtained in 65% yield.²

Hydrogenation of 4-methylpyrido[1,2-*a*]pyrimidinium bromide over platinum black gave the corresponding perhydro derivative as the hydrobromide salt.⁶

Methyl groups at positions 2 and/or 4 of the pyrido[1,2-*a*]pyrimidinium salts may be condensed with *p*-dimethyl-aminobenzaldehyde in acetic anhydride.^{3,4,13}

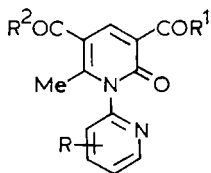
²⁵¹ Yu. V. Denisov, V. A. Puchkov, N. S. Vulfson, Z. E. Agadzhanian, V. K. Antonov, and M. M. Shemyakin, *Zh. Obshch. Khim.* **38**, 770 (1968) [*CA* **69**, 77718 (1968)].

The 2-methyl group of 2,6-dimethylpyrido[1,2-*a*]pyrimidinium perchlorate reacted readily with 3-methyl-2-methylthiobenzthiazolium methosulfate in the presence of triethylamine.³

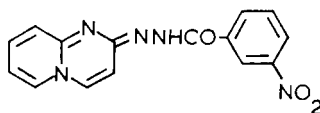
B. 2-Oxo-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

2-Oxo-2*H*-pyrido[1,2-*a*]pyrimidines are easily hydrolyzed to 2-amino-pyridines on heating with alkalis.²¹

Reaction of 2-oxopyrido[1,2-*a*]pyrimidines (**33**) with β -oxo esters in dimethylformamide in the presence of 1,5-diazabicyclo[4,3,0]non-5-ene at room temperature, or with β -oxo amides in the presence of zinc chloride in boiling ethanol, affords the pyridone derivatives (**199**). Cleavage of the pyrimidine ring can also be effected with amines.²⁸



$R^2 = \text{Oalkyl, NHAr}$
(199)



(200)

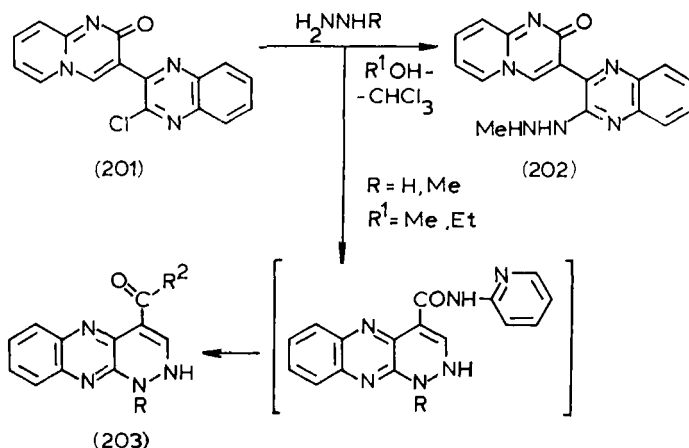
Hydrogenation of the 2-oxopyrido[1,2-*a*]pyrimidine over platinum(IV) oxide yielded the 2-oxoperhydro compound (**193**).²⁰⁰

Treatment of the 2-oxopyrido[1,2-*a*]pyrimidine (**22**; $R = H$) with triethyloxonium fluoroborate and subsequently with *m*-nitrobenzaldehyde gave the pyrido[1,2-*a*]pyrimidines (**200**). Hydrolysis of **200** with hydrochloric acid yielded 2-hydrazono-2*H*-pyrido[1,2-*a*]pyrimidine; following oxidative coupling with 1-hydroxy-2-naphthylamine or 4-acetylaminodiphenylamine, this was utilized for the preparation of azo dyes.²⁵²

Glushkov and Magidson reduced the nitroso group of 4-amino-3-nitroso-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (see also Section II,B) to a formylamino group with zinc powder in 50% formic acid. Intramolecular condensation of the latter with the 4-amino group yielded a pyrido[2,1-*a*]purinone.³⁰

Kurasawa and Takada transformed the 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (**30**) with phosphoryl chloride–dimethylformamide to the pyrido[1,2-*a*]pyrimidine (**201**) and reacted the latter with methylhydrazine to obtain 4% of the pyrido[1,2-*a*]pyrimidine (**202**) and 78% of the pyridazino[3,4-*b*]quinoxaline (**203**; $R = Me$, $R^2 = NMeNH_2$). Reaction with hydrazine gave the pyridazino[3,4-*b*]quinoxaline (**203**; $R = H$, $R^2 = OEt$).^{26,27}

²⁵² S. Hünig and K. H. Oette, *Justus Liebigs Ann. Chem.*, **640**, 98 (1961).



C. 4-Oxo-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

Most of the publications concerning the reactivity of pyrido[1,2-*a*]-pyrimidines deal with 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines and their tetrahydro derivatives. For easy survey this section is subdivided into eleven subsections.

1. Hydrolysis and Solvolysis

Chichibabin⁹⁶ was the first to observe that 4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidines hydrolyze under acidic and alkaline conditions and that resulting products are generally the parent 2-aminopyridines. The 1,8-naphthyridines, which are also derived from 2-aminopyridines and 1,3-bifunctional compounds, maintain their ring system unchanged under the same conditions. This fact of differing stabilities of the two ring systems toward hydrolysis was later recognized by many authors and utilized for identification of the products arising from 2-aminopyridines.^{79,98,112,126}

Hydrolysis and solvolysis of the product formed from the pyrido[1,2-*a*]-pyrimidine (**63**) with benzenediazonium chloride was studied by Snyder and Robison.^{253,254} Ring opening of **63** to give malonamides on the action of aromatic amines was also observed.²⁵⁵

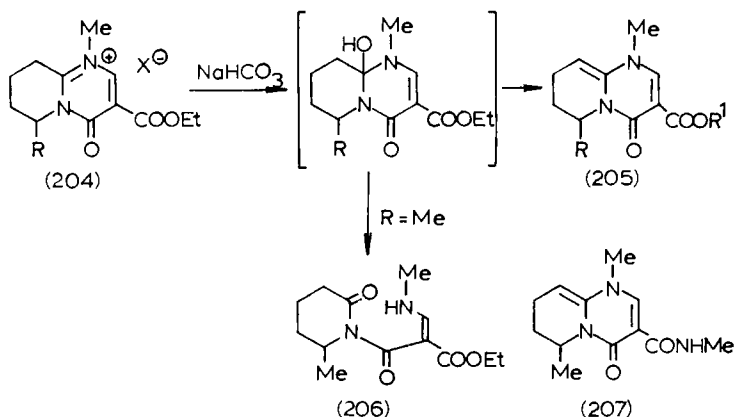
²⁵³ H. R. Snyder and M. M. Robison, *J. Am. Chem. Soc.* **74**, 4910 (1952).

²⁵⁴ H. R. Snyder and M. M. Robison, *J. Am. Chem. Soc.* **74**, 5945 (1952).

²⁵⁵ V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 209 (1958).

Depending on the reaction conditions, alkaline hydrolysis of the 3-alkoxycarbonylpyrido[1,2-*a*]pyrimidines (**71**) afforded the corresponding pyrido[1,2-*a*]pyrimidine-3-carboxylic acids,^{18,148} pyridylaminoacrylates (**73**; R = H)²⁵⁶ or 2-aminopyridines.¹²⁶ Acidic hydrolysis produced the half-ester of **70**.^{75,133,148}

From the quaternary salts of the 3-alkoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**71**), Landquist obtained the corresponding carboxylic acids by acidic hydrolysis and the 2-alkylaminopyridines by alkaline hydrolysis.¹³⁷ Ammonia generally cleaved the C-4—N-5 bond of the quaternary esters, except for the 7-nitro derivative in which the N-1—C-9a bond underwent cleavage.



Mészáros, Hermecz *et al.* transformed the quaternary 6,7,8,9-tetrahydro-pyrido[1,2-*a*]pyrimidinium salts (**204**) with acid to the carboxylic acids (**205**; $\text{R}^1 = \text{H}$)²⁵⁷ and with sodium hydrogen carbonate solution to the 1,6,7,8-tetrahydropyrido[1,2-*a*]pyrimidines (**205**; R = alkyl).^{75,258} From the alkaline hydrolysis reaction mixture, compounds **206** and **207** were also isolated.¹³³ The quaternary salt (**204**; R = Me) was transformed with hydrazine hydrate to 6-methylpiperidone and with ammonia to 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide and its *N*-methyl derivative.¹³³

Other reactions of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines accompanied by cleavage of the pyrimidine ring are discussed under the heading "Ring transformations" (Section III.C.10).

²⁵⁶ G. R. Lappin, *J. Am. Chem. Soc.* **71**, 3258 (1949).

²⁵⁷ Z. Mészáros, J. Knoll, P. Szentmiklósi, I. Hermecz, Á. Horváth, L. Vasvári-Debreczy, and T. Szűts, German Patent 2,729,721 [*CA* **88**, 121239 (1978)].

²⁵⁸ Z. Mészáros, *Kem. Kozl.* **50**, 173 (1978).

2. Hydrogenation, Reduction, Dehydrogenation, and Oxidation

Upon hydrogenation (over Pd/C or Raney nickel) the 4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidines were readily converted to the corresponding 6,7,8,9-tetrahydro derivatives.^{49,55,56,58,71,72,74–77,92,131,133,139,145–147,160,186,259–265} Under similar conditions^{75,133,266} or over platinum(IV) oxide,^{18,136} some derivatives containing an ester group in position 3 absorbed 3 mol of hydrogen, yielding the 1,6,7,8,9,9a-hexahydro compounds. Catalytic hydrogenation of the 9-alkoxycarbonyl- or aminocarbonylpyrido[1,2-*a*]pyrimidines resulted in a tautomeric equilibrium mixture of the 1,6,7,8- and 6,7,8,9-tetrahydro derivatives.^{55,58} Saturation of the pyridine ring was sometimes accompanied by hydrogenation of a double bond in the side chain attached to position 3²⁶⁰ or by debenylation of a benzylpiperazino group.^{49,263} 9-Carboxymethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines were converted by catalytic hydrogenation to the corresponding 9-acetic acids.^{266,267}

According to Kobayashi *et al.*,²⁶⁸ 4-oxo- and 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitriles can be reduced to the 6,7,8,9-tetrahydro compounds with sodium borohydride. Reduction of the hydroiodide of **41** (R = H) with sodium borohydride or lithium aluminum hydride, however, was unsuccessful.²

In the 6,7,8,9-tetrahydro derivatives containing a carboxylic ester or amide group in position 3, the C-9a=N-1 double bond was saturated by sodium

²⁵⁹ Z. Mészáros, J. Knoll, and P. Szentmiklósi, Hungarian Patent 156,119 [CA 71, 91520 (1969)].

²⁶⁰ T. George, C. L. Kaul, R. S. Grewal, and R. Tahilramani, *J. Med. Chem.* **14**, 913 (1971).

²⁶¹ I. Hermecz, Á. Horváth, J. Knoll, Z. Mészáros, and I. Vasvári-Debreczy, U.S. Patent 4,209,622 [CA 94, 30783 (1981)].

²⁶² Y. Sato, H. Takagi, S. Kumakura, and H. Fujita, Japan Kokai 77/05,796 [CA 87, 53358 (1977)].

²⁶³ Y. Sato, H. Takagi, S. Kumakura, and H. Fujita, Japan Kokai 77/05,797 [CA 87, 53359 (1977)].

²⁶⁴ Y. Sato, H. Takagi, S. Kumakura, and H. Fujita, Japan Kokai 77/05,795 [CA 97, 53360 (1977)].

²⁶⁵ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,195 [CA 91, 57053 (1979)].

²⁶⁶ I. Hermecz, Z. Mészáros, S. Virág, L. Vasvári-Debreczy, Á. Horváth, J. Knoll, G. Sebestyén, and Á. Dávid, German Patent 2,705,778 [CA 87, 201574 (1977)]; Belgian Patent 851,346 [CA 88, 10405 and 190880 (1978)]; Canadian Patent 1,082,699 [CA 94, 103412 (1981)].

²⁶⁷ I. Hermecz, Z. Mészáros, L. Vasvári-Debreczy, Á. Horváth, S. Virág, and J. Sipos, *Arzneim.-Forsch.* **29**, 1833 (1979).

²⁶⁸ G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, and C. Maseda, *J. Pharm. Soc. Jpn.* **94**, 44 (1974).

borohydride to give the 1,6,7,8,9,9a-hexahydropyrido[1,2-*a*]pyrimidines.^{74-78,131,133} This reaction failed to proceed if a methyl or a phenyl group was in position 3.¹⁴⁸ The charge density at C-9a as calculated by the CNDO/2 method and the reactivity of the molecule in the sodium borohydride reduction were found to be correlated.¹⁴⁸

Attempts to reduce the quaternary salts of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines with sodium borohydride or lithium aluminum hydride remained unsuccessful.¹³⁷ At the same time the 6,7,8,9-tetrahydro quaternary salts may readily be reduced with sodium borohydride to the 1-alkyl-1,6,7,8,9,9a-hexahydro derivatives.^{75,77,133,148,269,270} Sodium borohydride reduction of the 1,6- and 1,7-dimethyl-3-carbamoyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium salts proceeds stereoselectively and yields the thermodynamically controlled product.²⁷¹ The 1-methyl-3-carbamoyl-4-oxo-1,6,7,8,9,9a-hexahydropyrido[1,2-*a*]pyrimidines were also prepared by the catalytic (Pd/C) hydrogenation of the 1,6,7,8-tetrahydro derivatives,²⁷⁰⁻²⁷² but this reaction led to a diastereoisomeric mixture.²⁷¹

Hydrogenation of 6-methyl-4-oxo-4*H*-1,6,7,8,9,9a-hexahydropyrido[1,2-*a*]pyrimidine-3-carboxylic ester to the perhydro derivative was performed by catalytic (Pd/C) hydrogenation. The 1-methyl derivative was reduced by sodium borohydride.^{75,133}

Perhydropyrido[1,2-*a*]pyrimidin-4-one was prepared from the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine by hydrogenation over platinum(IV) oxide¹⁸ or from the 2-chloro derivative by use of Pd/C catalysts.¹³⁹

By hydrogenating 2,9-disubstituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines or their 6,7,8,9-tetrahydro derivatives over platinum(IV) oxide, Yale and Spitzmiller obtained a mixture of diastereomeric perhydro compounds.⁵⁸ Separation was not attempted.

Schulte and Witt hydrogenated the pyrido[1,2-*a*]pyrimidines (**63**: R = H or 8-Me) containing a but-2-ynyl group in position 3 over Lindlar's or Pd/CaCO₃ catalysts and reported the formation of the 3-(but-2-enyl) and 3-butyl derivatives, respectively.¹⁰³ The melting point of the compound reported to be the 8-methyl-3-butyl derivative, however, differed by 20°C from the melting point of the 3-butyl derivative of **63** (R = 8-Me), later obtained by Klosa¹¹¹ via direct synthesis. Schulte and Witt¹⁰³ reported that the 3-propyl derivative of **63** (R = H) absorbed 2 mols of hydrogen in the

²⁶⁹ Z. Mészáros, J. Knoll, and P. Szentmiklósi, HUNG. TELJES **519** [CA **74**, 42374 (1971)].

²⁷⁰ Z. Mészáros, J. Knoll, P. Szentmiklósi, I. Hermecz, Á. Horváth, G. Nagy, S. Virág, L. Vasvári-Debreczy, and Á. Dávid, German Patent 2,728,198 [CA **88**, 121237 (1978)].

²⁷¹ T. Breining, I. Hermecz, Z. Mészáros, G. Tóth, and M. Kajtár, *Magy. Kem. Lapja* **33**, 432 (1968) [CA **90**, 54852 (1979)].

²⁷² Z. Mészáros, J. Knoll, P. Szentmiklósi, I. Hermecz, Á. Horváth, G. Nagy, S. Virág, L. Vasvári-Debreczy, and Á. Dávid, HUNG. TELJES **T/17,187** [CA **92**, 163997 (1980)].

presence of Pd/CaCO_3 , but the structure of the product has not been elucidated.

Hydrogenation of the 1-propargyl and 1-allyl derivatives of **63** ($\text{R} = \text{H}$) over Pd/CaCO_3 or Pd/C gave the 1-propyl compound,^{103,273} whereas 2-propargyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine yielded the 2-propyloxy compound.²⁷³ Catalytic hydrogenation of the 2-alkoxy- and 2-aralkoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was accompanied by the hydrogenolysis of the substituents in position 2.^{112,114}

Hydrogenation of **63** ($\text{R} = \text{H}$) at 60°C and 3 atm pressure over platinum(IV) oxide resulted in the 2,4-dioxoperhydro derivative.²⁷⁴ This was then dehydrogenated²⁷⁵ in *p*-cymene in the presence of Pd/C to the 6,7,8,9-tetrahydro derivative of **63** ($\text{R} = \text{H}$) or reduced with lithium aluminum hydride to perhydropyrido[1,2-*a*]pyrimidine.^{276,277}

Oxidation of the 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines and their hydroiodide salts with potassium permanganate yielded 6-substituted 4(3*H*)pyrimidinones.^{2,34}

3. Salt Formation, Quaternization, *N*-Alkylation, and *N*-Acylation

4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidines and their 6,7,8,9-tetrahydro derivatives readily form salts with inorganic and organic acids^{54,58,76} and quaternary salts on the N-1 atom on the action of alkylating agents.^{2,74-77,131,133,137,148-150,142,261,269,271,278,279}

Nevertheless, the 9-methyl derivative of **71** failed to produce a quaternary salt because of the steric hindrance effect of the methyl group,¹³⁷ as did 2-methyl-3-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine³⁷ because of the electron deficiency of the ring. When the pyridopyrimidine bore a substituent containing a nitrogen atom more basic than N-1, the quaternization occurred in that side chain.⁴²

4-Thioxo-4*H*-pyrido[1,2-*a*]pyrimidines are alkylated by methyl iodide at the sulfur atom and not at the N-1 atom.^{2,71} Alkylation and acylation of 1,6,7,8,9,9a-hexahydropyrido[1,2-*a*]pyrimidines led to the 1-alkyl^{75-77,148,269-272} and 1-acyl derivatives.^{136,280}

²⁷³ A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1544 (1962).

²⁷⁴ V. Boekelheide and J. Figueras, *J. Am. Chem. Soc.* **71**, 2587 (1949).

²⁷⁵ A. R. Katritzky, F. D. Popp, and A. J. Waring, *J. Chem. Soc., B*, 565 (1966).

²⁷⁶ R. L. Peck, *Diss. Abstr. B* **29**, 114 (1968) [*CA* **70**, 4038 (1969)].

²⁷⁷ R. L. Peck and A. R. Day, *J. Heterocycl. Chem.* **6**, 181 (1969).

²⁷⁸ L. G. S. Brooker and F. G. Webster, U.S. Patent 3,539,349 [*CA* **75**, 7444 (1971)].

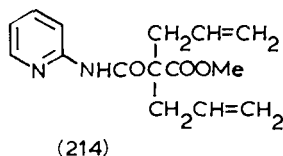
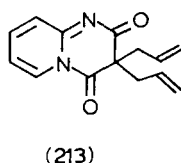
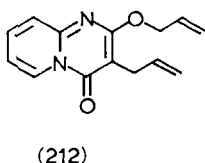
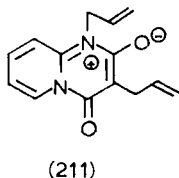
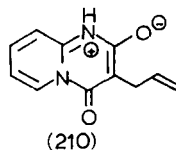
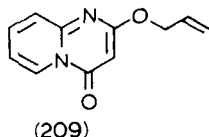
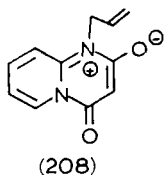
²⁷⁹ J. M. Chemerda and G. Gal, British Patent 1,348,414 [*CA* **81**, 152262 (1974)].

²⁸⁰ Z. Mészáros, J. Knoll, P. Szentmiklósi, and I. Hermecz, German Patent 2,320,377 [*CA* **80**, 27278 (1974)].

4. Alkylation and Acylation of Anhydro-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimid-1-inium)hydroxides

Alkylation has been carried out with alkyl halides in methanolic alkali metal methoxide,^{98,103,104,112,114,273} in aqueous ethanolic solution of potassium hydroxide and potassium iodide,^{106,281} and in dimethylformamide in the presence of potassium carbonate.¹¹⁴ Alkylation generally led to more than one product.

Schulte and Witt¹⁰³ described the products obtained from the pyrido[1,2-*a*]pyrimidine (**63**; R = H) with propargyl bromide and with 1-bromo-2-yne in methanolic potassium methoxide as the 2-alkoxy derivatives (mp = 200°C). Later, Katritzky and Waring²⁷³ proved these compounds to be the 1-alkyl derivatives. From **63** (R = H) with methyl iodide they obtained the 1-methyl derivative; with propyl bromide, the 2-propyloxy derivative; and with propargyl bromide, a mixture of the 1-propargyl and 2-propyloxy derivatives.



Urban *et al.*¹¹² obtained the monoallyl (**208–210**) and the diallyl (**211** and **212**) derivatives from the pyrido[1,2-*a*]pyrimidine (**63**; R = H) with allyl

²⁸¹ Y. Yoshioka, R. Marumoto, M. Honjo, and K. Kikuchi, German Patent 2,131,938 [CA 76, 99994 (1972)].

bromide in methanolic sodium methoxide. When subjected to similar conditions, the 3-allyl derivative (**210**) furnished the *N,C*- and *O,C*-diallyl compounds (**211** and **212**) and also a ring-cleaved product (**214**), resulting from methanolysis of the *C,C*-diallyl derivative (**213**). Similarly, on benzylating the 3-benzyl derivative of **63** (*R* = H), Kappe *et al.*¹¹⁴ likewise obtained ring-cleaved products and not the 3,3-dibenzyl derivative. The instability of the 3,3-disubstituted derivatives of type **213** is in accordance with the observation that 3,3-disubstituted 2,4-dioxo-4*H*-pyrido[1,2-*a*]pyrimidines cannot be prepared from the reaction of 2-aminopyridine and disubstituted malonic esters⁹⁶ or malonyl chlorides.³⁵

Kotarska *et al.*^{106,282} attributed the 3-substituted structures to the products obtained from the pyrido[1,2-*a*]pyrimidine (**63**: *R* = H) by alkylation with either 1-chloromethylnaphthalene or allyl bromide, or with benzyl chloride in ethanolic potassium hydroxide in the presence of potassium iodide. The melting point of the 3-benzyl compound agreed with the earlier literature datum but that of the 3-allyl compound differed by more than 20°C.^{100,112}

Ingalls and Popp⁹⁸ reported that the 7- and 8-methyl derivatives of **63** (*R* = H) gave the corresponding 1-methyl compounds with methyl iodide, whereas the 9-methyl derivative failed to react, probably due to steric hindrance.

Allen prepared several 2-(*ω*-dialkylaminoalkoxy)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines by reacting the 3-substituted derivatives of **63** (*R* = H) with dialkylaminoalkyl halides.¹⁰⁴ 3-Substituted pyrido[1,2-*a*]pyrimidines (**63**: *R* = H) have also been treated with methyl iodide⁹⁸ and methyl sulfate,²⁷⁸ but the structures of the products have not been elucidated.

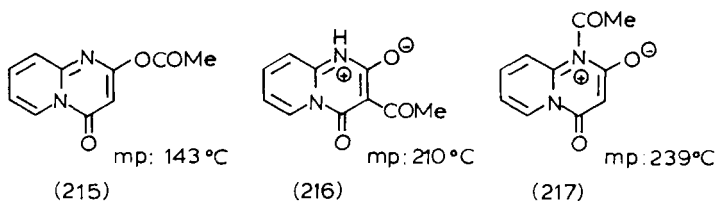
Schindler *et al.*¹¹⁶ heated the 1-benzyl derivative of **63** (*R* = H) under nitrogen at 250–260°C and obtained 2-benzyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine in 10% yield.

Acylation of compounds of type **63** was carried out with acid anhydrides,¹⁰⁷ occasionally in the presence of sodium acetate.^{103,282} Acylation was also carried out with acid chlorides in benzene or chloroform, and either in the presence of pyridine^{121,282} or in the presence of potassium hydrogen carbonate.⁵¹ Reactions starting from the sodium salt of **63** (*R* = H) were also carried out.¹⁶⁷ The formation of more than one product has usually been reported.

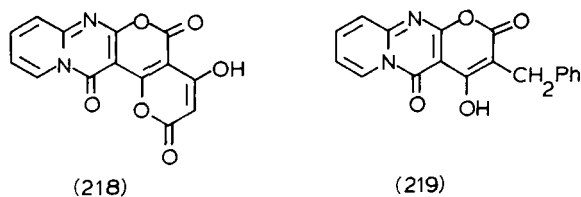
Schulte and Witt^{51,103} used acetic anhydride, whereas Yale used benzoyl chloride to prepare 2-acyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines from **63** (*R* = H). Kappe *et al.*¹⁰⁷ obtained the 2,9-diacetoxy compound from **63** (*R* = 9-OH).

²⁸² A. Kotarska, S. Staniszevska, and L. Kociszewski, *Soc. Sci. Lodz., Acta Chim.* **16**, 89 (1971) [*CA* **77**, 34448 (1972)].

Dashkevich and Kuvaeva¹²¹ assumed that the products arising from **63** ($R = H, Me$) with acetyl chloride or *p*-nitrobenzoyl chloride were 4-acyloxy-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines. This assignment is not likely to be correct, however, for Kato and Masuda¹⁶⁷ demonstrated that the 2-acetoxy (**215**: mp = 143°C) and the 3-acetyl (**216**: mp = 210°C) derivatives were formed from the sodium salt of **63** ($R = H$) with acetyl chloride. The acetylated product obtained by Dashkevich and Kuvaeva from **63** ($R = H$) melted at 152–154°C, and thus it might well have been **215** or a mixture of **215** and **216**.



Kotarska *et al.*²⁸² postulated that the products formed from the pyrido[1,2-*a*]pyrimidine (**63**: $R = H$) with acetic anhydride in the presence of sodium acetate were the 3-acetyl compound (**216**: mp = 158–160°C) and the 1-acetyl compound (**217**: mp = 239–242°C), but no evidence for these structures was put forward. The products obtained from **63** ($R = H$) with benzoyl and *p*-nitrobenzoyl chloride were described as 3-acyl derivatives, but since they melted below 200°C, the 2-acyloxy structure of type **215** should also be considered.



Ziegler *et al.*¹¹³ reported that the reaction of **63**: $R = H$) with bis-2,4-dichlorophenyl malonate at 230°C gave the tetracyclic compound (**218**), while with bis-2,4-dichlorophenyl benzylmalonate at 200°C the tricyclic compound (**219**) was formed. This means that the acylation involved both the O-2 atom and the C-3 atom of the ring system. French workers transformed the pyrido[1,2-*a*]pyrimidines (**63**: $R = H$) with dialkyl chlorothiophosphate or its monoamide to 2-acyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines.^{108,179,180}

5. Reactions Involving the C-2 Atom or the 2-Substituent of Pyrido[1,2-*a*]pyrimidines

The C-2 atom of the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines is usually reactive in nucleophilic substitutions.

Anhydro-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimid-1-inium)hydroxides undergo transformation to 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines on being heated in phosphoryl chloride.^{98,112,253,255,283} On the action of a mixture of phosphoryl chloride and phosphorus pentachloride, the 2,3-dichloro derivatives were formed if the 3-position of the substrate was unsubstituted.²⁵⁴ 2-Chloro derivatives were also prepared from the 2-methoxy derivatives of the unsaturated pyrimidines and the 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines under the conditions of the Vilsmeier–Haack formylation.^{98,284}

The 2-chloro substituent may be exchanged for various nucleophiles. The 2-alkoxy derivatives were formed with alkali metal alkoxides,^{98,112,255,273} the 2-amino derivatives were formed with ammonia and amines,^{79,98,255,260,283,285,286} the 2-hydrazino derivatives were formed with hydrazine,^{98,255,283,287} and the 2-thiocyanato derivatives were formed with alkali metal thiocyanates.²⁸³ 2,3-Dichloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine in phenol reacts with gaseous ammonia to yield a mixture of the 2-phenoxy and 2-amino derivatives, whereas with sodium hydroxide, the 2-phenoxy compound is obtained.²⁵⁵

Another way to prepare 2-amino derivatives is by the reaction of 2-methylthio-4-oxo-4*H* derivatives with amines.^{268,288} The 2-methylthio-4-imino derivative reacted differently (see Section III.C.8). 2-Amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine could have also been prepared by reducing the 2-hydrazino derivative with hydrogen sulfide.²⁸⁹

Diethyl malonate in methanol in the presence of potassium carbonate transformed the 2-methylthio group of **93** (X = O) into a 2-methoxy group. If the solvent was dimethylformamide, the product was the malonic acid derivative (**220**).²⁶⁸ 2-Methoxy-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine was prepared from the corresponding 2-methylthio derivative (**93**: X = NH) by treatment with methanolic sodium hydroxide.²⁶⁸

²⁸³ E. Winkelmann, W. Röther, H. Hartung, and W. H. Wagner, *Arzneim.-Forsch.* **27**, 82 (1977).

²⁸⁴ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,192 [*CA* **91**, 107997 (1979)].

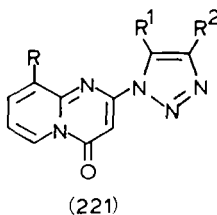
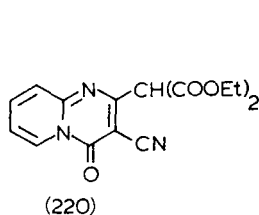
²⁸⁵ T. George, D. V. Mehta, and D. A. Dabholkar, *J. Org. Chem.* **36**, 2192 (1971).

²⁸⁶ A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 2828 (1970).

²⁸⁷ A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 3811 (1970).

²⁸⁸ G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *J. Pharm. Soc. Jpn.* **89**, 203 (1969).

²⁸⁹ B. Stanovnik, M. Tisler, S. Polanc, V. Kovacic-Bratina, and B. Spicer-Smolnikov, *Tetrahedron Lett.*, 3193 (1976).



Hydrolysis of the 2-acetylthioxy derivative (**103**; X = S) in aqueous methanol gave the 2-mercapto derivative, which was then desulfurized to 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine in 3% aqueous ammonia in the presence of Raney nickel.¹⁶⁷ The same product was obtained in poor yield when 2-hydrazino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was treated with a 15% solution of copper(II) sulfate in aqueous acetic acid.²⁵⁵

The 2-amino group of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines can be transformed to a hydroxy group by sodium nitrite in concentrated sulfuric acid at 0°C.²⁵⁵ The 2-hydroxy group can be formed from the 2-mercapto group by treatment with 3% hydrogen peroxide in 1*N* potassium hydroxide.¹⁶⁷

The hydrazino group of 2-hydrazino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was alkylated at N-2 with 6-chloronebularine,²⁸¹ formylated at N-2 by heating in formic acid,¹⁶⁶ and transformed to a Schiff's base by reaction with benzaldehyde.¹⁶⁶

2-Hydrazono-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines were transformed by sodium nitrite in hydrochloric acid at 0–5°C to the corresponding 2-azido compound (**102**).^{166,287} 2-Azido-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine does not exhibit azide–tetrazole tautomerism.²⁹⁰

As part of their study on aza-transfer reactions, Tisler and co-workers^{289,290} reacted 2-hydrazino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine with various diazo derivatives and obtained 2-azido- and 2-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines. From 2-azido-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines various derivatives of 2-(1,2,3-triazol-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**221**) were prepared by reaction with acetylene,²⁸⁷ 1,3-dioxo compounds,¹⁶⁶ or diethylamine.²⁹¹ For further ring transformation reactions of the 2-azido-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**102**), see Section III.C.10.

The 2-methyl group of 2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**41**) and their 6,7,8,9-tetrahydro derivatives can be condensed with aromatic and heteroaromatic aldehydes in the presence of methanolic sodium methoxide.^{57,60,292}

²⁹⁰ L. Dezman, D. Janežic, M. Kokaly, E. Kozak, J. Princ, B. Stanovnik, M. Tisler, and D. Zaplotnik-Naglic, *Tetrahedron* **33**, 2851 (1977).

²⁹¹ S. Polanc, B. Stanovnik, and M. Tisler, *J. Org. Chem.* **41**, 3152 (1976).

²⁹² H. L. Yale and E. R. Spitzmiller, *J. Heterocycl. Chem.* **13**, 869 (1976).

In 2,8-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine the 8-methyl group also can be condensed with aldehydes, though less readily than the 2-methyl group.²⁹² The *E* configuration of the newly formed double bonds has been proved by ¹H-NMR spectroscopy.

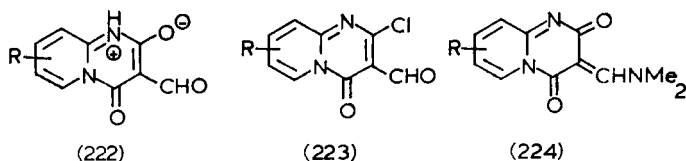
6. Reactions Involving the C-3 Atom or the 3-Substituent of Pyrido[1,2-*a*]pyrimidines

The C-3 atom of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines readily takes part in electrophilic substitutions. 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidines unsubstituted at position 3 may be transformed by nitrating agents to the 3-nitro derivatives^{37,42,52,96,116,293} and by halogenating agents to the 3-halo derivatives.^{18,34,108,253,255,294} Nitration of 2-benzyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was accompanied by debenzylation.¹¹⁶ Halogenation of the pyrido[1,2-*a*]pyrimidine (**63**; R = H) under forced conditions afforded the 2,3-dichloro derivatives.^{253,255}

With aryldiazonium chlorides the pyrido[1,2-*a*]pyrimidines (**63**; R = H) yielded the 3-arylazo derivatives.²⁵³ The 3-methyl derivative of **63** (R = H) was also subjected to diazo coupling, but the product, a 3,3-disubstituted pyrido[1,2-*a*]pyrimidine, underwent immediate transformation involving hydrolysis of the C-4—N-5 bond²⁵³ (see also Section III.C.4).

3-Aminomethylene derivatives may be prepared by reacting the pyrido[1,2-*a*]pyrimidines (**63**; R = H) with aminomethanols in ethereal hydrogen chloride solution or with amines and paraformaldehyde.²⁹⁵

Depending upon the reaction conditions, Vilsmeier–Haack formylation of the pyrido[1,2-*a*]pyrimidines (**63**; R = H, Me) yielded the 3-formyl derivatives (**222** and **223**) or the 3-dimethylaminomethylene compounds (**224**).^{98,285,296–298} Under vigorous conditions, 2-methoxy-4-oxo-4*H*-pyrido



²⁹³ D. R. Buckle, B. C. C. Cantello, H. Smith, and B. Y. Spicer, *J. Med. Chem.* **18**, 726 (1975).

²⁹⁴ R. Adams and I. J. Pachter, *J. Am. Chem. Soc.* **76**, 1845 (1954).

²⁹⁵ E. Ziegler and E. Kiesewetter, *Monatsh. Chem.* **96**, 659 (1965).

²⁹⁶ C. H. Eldredge and J. D. Mee, French Demande 2,027,006 [*CA* **75**, 50420 (1971)].

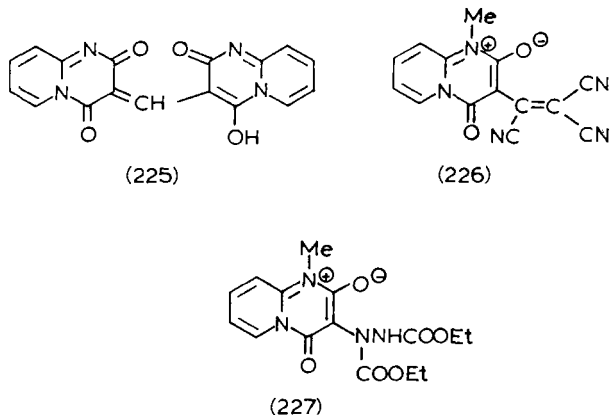
²⁹⁷ C. H. Eldredge and J. D. Mee, U.S. Patent 3,674,782 [*CA* **77**, 128093 (1972)].

²⁹⁸ C. H. Eldredge and J. D. Mee, French Patent 1,565,255 [*CA* **73**, 89163 (1970)].

[1,2-*a*]pyrimidine gave **223** ($R = H$), whereas under mild conditions the 3-formyl-2-methoxy derivative was produced.⁹⁸ 4-Oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines unsubstituted at position 3 yielded the 3-formyl derivatives under vigorous conditions.²⁸⁴

The pyrido[1,2-*a*]pyrimidine (**63**; $R = H$) gave the 3-anilinomethylene derivative of type **224**²⁹⁹ with ethyl *N*-phenylformimidate, and it gave the bis compound (**225**) with triethyl orthoformate in a dimethylformamide-acetic acid mixture.³⁰⁰ The exact structure of **225** has not been elucidated.

The C-3 atom of the pyrido[1,2-*a*]pyrimidine (**63**; $R = H$) reacted with *N,N'*-diphenylformamidine in acetic anhydride³⁰¹ and with naphtholactam in phosphoryl chloride.³⁰² Compound **63** ($R = 8\text{-Me}$) reacted at position 3 with various benzothiazolium salts in the presence of bases.¹⁰⁹ Under more drastic conditions the 8-methyl group also reacted.



With tetracyanoethylene the 1-methyl derivative of **63** ($R = H$) led to compounds of type **226**; with diethyl azodicarboxylate, to compounds of type **226**; and with diethyl azodicarboxylate, to compounds of type **227**.¹¹⁴ The 3-formyl and the 3-aminomethylene group of the pyrido[1,2-*a*]pyrimidines (**222**; $R = H$ and **224**) underwent condensation with compounds containing an active methylene group.^{297-299,303} The 3-formyl group has also been reacted with primary amines,²⁸⁵ hydrazines,^{98,260,285} semicarbazide and thiosemicarbazide.⁹⁸

²⁹⁹ F. G. Webster and D. W. Heseltine, French Patent 1,577,440 [*CA* **73**, 20441 (1970)].

³⁰⁰ O. S. Wolfbeis and H. Junek, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **31B**, 95 (1976).

³⁰¹ A. W. Anish, U.S. Patent 2,423,218 [*CA* **41**, 6584 (1947)].

³⁰² E. Schefczik, German Patent 2,924,067 [*CA* **94**, 141204 (1981)].

³⁰³ G. F. Mitchell, German Patent 2,028,861 [*CA* **75**, 13530 (1971)].

3-Formyl-2-methylamino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was prepared from the corresponding Schiff bases by acidic hydrolysis. The 3-formyl group was condensed with methylhydrazine, and various transformations were then carried out at the N-2 atom.²⁸⁵

The 3-ester group of the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines and their hydrogenated derivatives have been hydrolyzed^{18,74,75,78,133,137,148,266,267,304–308} and amidated,^{74–77,133,137,148,155,270–272,306,307}

The carboxylic acids have been esterified^{131,154} and decarboxylated.^{18,74,75,131,133,261,308,309} 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids were prepared from the corresponding amide¹⁶⁰ and nitrile¹⁵⁶ by acidic hydrolysis.

The 3-ester group of quaternary pyrido[1,2-*a*]pyrimidinium salts was hydrolyzed under acidic conditions^{137,257} (see also Section III.C.1).

Hydrolysis of the homologous esters has been reported but the direct amidation of these esters failed.^{131–133,261} The 3-acetamide derivative was prepared from the corresponding hydrazide with the aid of Raney nickel.^{131,133}

4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide was also prepared from the 3-nitrile.²⁶⁸ *N*-substituted carboxamides were obtained from the carboxylic acids and amines by known procedures.^{131,141,261,310–313} 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidines unsubstituted at position 3 were prepared from the 3-carboxamides, 3-nitriles,²⁶⁸ and 3-acetyl derivatives.¹⁶⁸

The 3-ester group was transformed by transesterification,²⁶⁶ by hydrazinolysis,^{131,133,136,137,261,307} and by reaction with hydroxylamine.^{74,75}

4-Oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide was *N*-acylated,⁷⁵ and the *N*-methyl derivative was *N*-formylated.²⁸⁴

The 3-carboxamides were dehydrated to the 3-nitriles.^{79,255,284} The 3-nitrile group of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was transformed with sodium azide to a tetrazolyl group.¹⁵⁵ The 3-carbazoyl group was acylated at N-2,¹³⁸ and in the 6,7,8,9-tetrahydro series, it was transformed to a —CONHN=CH—NMe₂ group²⁸⁴ or condensed with aldehydes.²⁶⁶

³⁰⁴ H. Öhlschläger, O. Riester, and A. Dorlars, German Patent 2,132,937 [CA 78, 104458 (1973)].

³⁰⁵ G. Takáts, *Acta Pharm. Hung.* 47, 97 (1977) [CA 87, 126816 (1977)].

³⁰⁶ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,193 [CA 91, 74647 (1979)]; Netherlands Patent Appl. 79/03, 401 [CA 95, 220079 (1981)].

³⁰⁷ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,194 [CA 91, 91658 (1979)].

³⁰⁸ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,141 [CA 91, 175382 (1979)].

³⁰⁹ J. Volford, Z. Mészáros, and G. Kovács, *J. Labelled Compd.* 9, 231 (1973).

³¹⁰ M. Murakami, I. Isaka, A. Koda, N. Kawahara, T. Kashiwagi, M. Ageo, U. Yukiyasu, K. Yano, K. Nakano, and I. Souzu, German Patent 2,322,750 [CA 80, 70803 (1974)].

³¹¹ Z. Mészáros, J. Knoll, P. Szentmiklósi, I. Hermecz, Á. Horváth, S. Virág, L. Vasvári-Debreczy, and Á. Dávid, German Patent 2,653,257 [CA 87, 135383 (1977)].

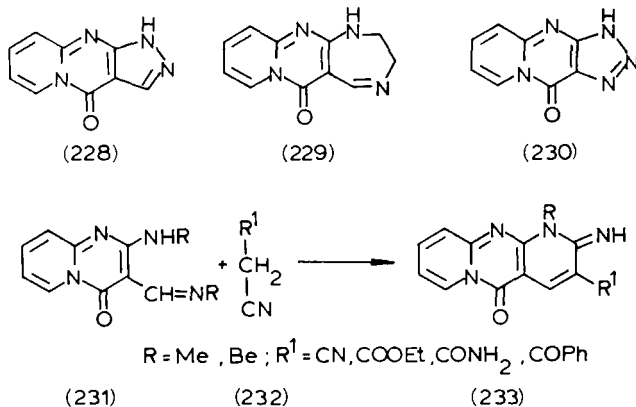
³¹² P. F. Juby, German Patent 2,913,295 [CA 92, 111049 (1980)].

³¹³ T. Kamiya, T. Teraji, K. Kemmi, and J. Goto, German Patent 2,737,066 [CA 88, 190866 (1978)].

The hydroxy group of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-alcohols may be exchanged for a halogen atom^{49,65,264} or transformed to a tosyloxy^{49,66} or acyloxy group.⁴⁹ The 3-chloro substituent was exchanged for the amino group by Gabriel synthesis, the amine was acylated with 4-acetamidobenzenesulfonyl chloride, and the acetamido group was hydrolyzed.⁶⁵ In the side chain at position 3 the chlorine atom or the tosyloxy group was reacted with amines,^{49,66,70,83,262-264} and the amino group was acylated^{49,263} or alkylated.⁴⁹ Addition of water to a double bond in the side chain was also carried out.⁴⁹

7. Cyclizations Involving Positions 2 and 3 of the Pyrido[1,2-*a*]pyrimidines

2-Chloro-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was transformed with hydrazine and ethylenediamine, respectively, to the tricyclic compounds **228**⁹⁸ and **229**.²⁸⁵ Treatment of 2,3-diamino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines with sodium nitrite in aqueous acetic acid afforded the pyrido[1,2-*a*]-*v*-triazolo[4,5-*d*]pyrimidines (**230**).³¹ Reaction of the pyrido[1,2-*a*]pyrimi-



dines (**231**) with the nitriles (**232**) gave the tricyclic derivatives (**233**).²⁸⁵ For additional cyclizations involving positions 2 and 3 of pyrido[1,2-*a*]pyrimidines, see also Section III.C.4.

8. Reactions Involving Atom C-4 of the Pyrido[1,2-*a*]pyrimidine Ring and Cyclizations Involving Positions 4 and 6

The 4-oxo-group of the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was transformed to a thioxo group by diphosphorus pentasulfide in pyridine,^{2,49,71} Under similar conditions the oxygen to sulfur exchange could not be achieved

with 3-ethyl-2,6-dimethyl- and 2,3-diphenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines.^{71,173} The 4-thioxo derivatives may be converted to 4-methylthiopyrido[1,2-*a*]pyrimidinium iodides with methyl iodide.^{2,71}

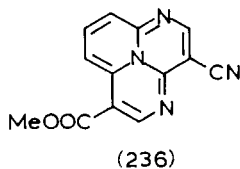
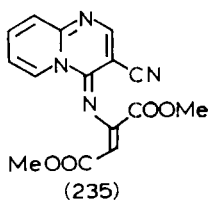
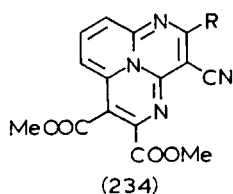
The thioxo group of 2,3-diphenyl-4-thioxo-4*H*-pyrido[1,2-*a*]pyrimidine was converted with mercuric acetate to an oxo group.^{172,173} The imino group of 4-imino-4*H*-pyrido[1,2-*a*]pyrimidines was hydrolyzed with acids to an oxo group.^{156,268}

The 4-imino group of 3-cyano-4-imino-2-methylthio-4*H*-pyrido[1,2-*a*]pyrimidine was transformed to the 4,4-diamino group with amines and to the 4-methylimino group with methyl iodide in dimethylformamide in the presence of potassium carbonate.²⁶⁸ On the action of dimethyl acetylenedicarboxylate in dimethylformamide at 150°C, the 1,4-diazacycl[3,3,3]azine (**234**; R = CH₃S) was formed.³¹⁴

3-Cyano-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine and dimethyl acetylenedicarboxylate in xylene in the presence of 5% Pd/C as catalyst yielded the pyrido[1,2-*a*]pyrimidine (**235**) and the 1,4-diazacycl[3,3,3]azine (**234**; R = H). With methyl propiolate the product was the 1,4-diazacycl[3,3,3]azine (**236**).³¹⁴ Treatment of **235** with 5% Pd/C resulted in 1,4-diazacycl[3,3,3]azine (**234**; R = H).³¹⁵

9. Reactions Involving the C-9 Atom or the 9-Substituent of the Pyrido[1,2-*a*]pyrimidines

Bromination of ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate in carbon tetrachloride yielded the 9-bromo derivative.⁷⁵



³¹⁴ H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *J. Pharm. Soc. Jpn.* **95**, 13 (1975).

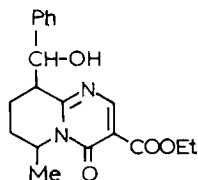
³¹⁵ M. Kuya, K. Kasata, H. Awaya, K. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **26**, 680 (1978).

6,7,8,9-Tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines contain an active methylene group in position 9, which permits versatile transformations.¹⁴⁸

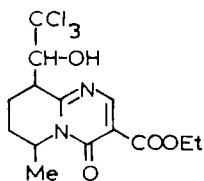
Depending on the molar ratio, halogenation of 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines gave 9-halo or 9,9-dihalo compounds.^{75,133,316–319} 9-Bromo- or 9-chloro-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids were obtained as 4:1 mixtures of the thermodynamically more stable 6,9-diaxial and the 6-axial, 9-equatorial-substituted diastereoisomers.³¹⁷

On catalytic hydrogenation the 9-bromo group is eliminated.⁷⁵

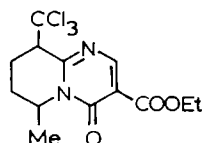
With aromatic and heteroaromatic aldehydes,¹⁹³ 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines yielded the 9-arylmethylene derivatives,^{133,266} whereas with glyoxylic acid the 9-carboxymethylene derivative was formed.^{266,267} The primary addition product (**237**) could be isolated from the reaction mixture of ethyl 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and benzaldehyde. On dehydration the addition product (**237**) gave the 9-benzylidene compound.²⁶⁶ The 9-carboxymethylene derivatives may be transformed by catalytic hydrogenation to the 9-acetic acids, which can be esterified.^{266,267}



(237)



(238)



(239)

Reaction of ethyl 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and trichloroacetaldehyde afforded the addition product (**238**) below 40°C and the substitution product (**239**) at a higher temperature.¹³³

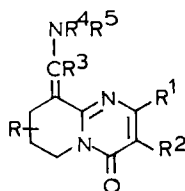
Depending on the work-up conditions, Vilsmeier–Haack formylation of 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines gave various 9-substituted pyrido[1,2-*a*]pyrimidines (**240–242**).^{284,319} The 9-aminomethylene derivatives (**240**) were transformed by hydrolysis in 0.5 *N* hydrochloric acid to the 9-formyl compounds (**241**: $R^3 = H$), by ethanolic hydrogen chloride to

³¹⁶ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 873,191 [*CA* **91**, 91657 (1979)].

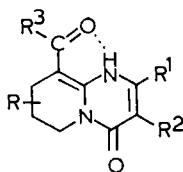
³¹⁷ I. Hermecz, T. Breining, G. Tóth, I. Bitter, and Z. Mészáros, *Heterocycles* **14**, 1953 (1980).

³¹⁸ I. Hermecz, T. Breining, L. Vasvári-Debreczy, Á. Horváth, Z. Mészáros, I. Bitter, and J. Kökösi, German Patent 3,017,564 [*CA* **94**, 121591 (1981)].

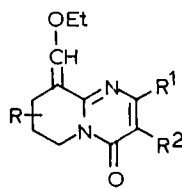
³¹⁹ I. Hermecz, I. Bitter, Á. Horváth, G. Tóth, and Z. Mészáros, *Tetrahedron Lett.*, 2557 (1979).



(240)



(241)



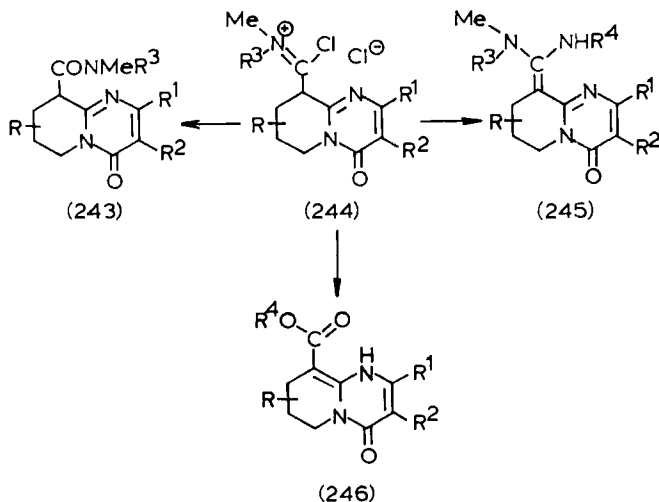
(242)

the ethoxymethylene derivatives (**242**), and by anilines to the 9-anilino-methylene derivatives. The 9-formyl derivatives (**241**: $R^3 = H$) reacted with amines to give the 9-aminomethylene derivatives (**240**).

Hydrolysis of the 9-ethoxymethylene derivatives in 0.5 *N* hydrochloric acid yielded the formyl compounds (**241**: $R^3 = H$), which reacted with amines to provide the 9-aminomethylene derivatives (**240**). The 9-aminomethylene derivatives (**240**) were also prepared by reacting 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines with *N,N*-dimethylformamide diethyl acetal, or *N,N'*-diphenylformamidine, or with a mixture of an aromatic amine and an ortho ester. 9-Ethoxymethylene derivatives (**242**) also were prepared by reacting 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine with triethyl orthoformate in acetic anhydride.

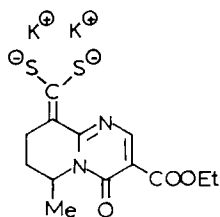
Treatment of the 9-formyl derivatives (**241**: $R^3 = H$) with thionyl chloride gave 9-chloromethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines, which were then transformed with ammonium thiocyanate to the 9-thiocyanatomethylene derivatives.²⁸⁴

In the reaction of 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines and phosgene iminium chloride, the 9-substituted pyrido[1,2-*a*]pyrimidines

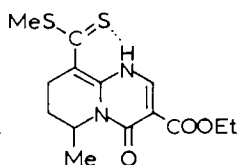


(**244**) were formed, which were then transformed with amines to the 9-diaminomethylene derivatives (**245**), with alcohols to the 9-carboxamides (**243**),³⁰⁶ and with alcohols and sodium acetate to the 9-esters (**246**).^{306,319}

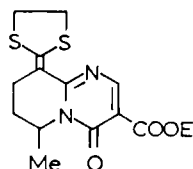
With carbon disulfide and ethanolic potassium hydroxide, ethyl 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine gave the dipotassium salt (**247**), which was methylated with dimethyl sulfate to the 9-methylthiothiocarbonyl compound (**248**) and alkylated with 1,2-dibromoethane to the



(247)

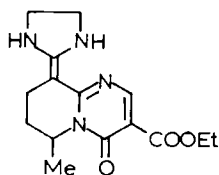


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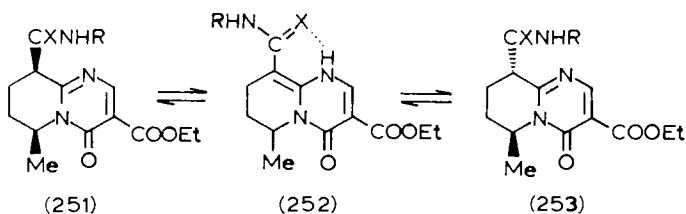
(249)

9-ketene mercaptal (**249**).³⁰⁶ The 9-imidazolidine derivative (**250**) was prepared from **248** or from the appropriately substituted pyrido[1,2-*a*]pyrimidine (**244**) with ethylenediamine.³⁰⁶



(250)

Ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate was alkylated at position 9 with isocyanates and isothiocyanates, occasionally in the presence of sodium hydride.^{306,320} The 9-carbamoyl compounds exhibited triple tautomerism between forms **251** and **253**.³²⁰



(251)

(252)

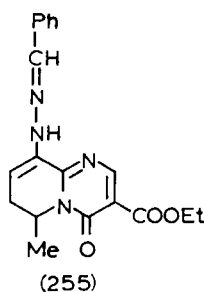
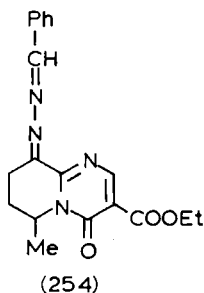
(253)

³²⁰ I. Bitter, I. Hermecz, G. Tóth, P. Dvortsák, and Z. Mészáros, *Tetrahedron Lett.*, 5039 (1979).

9-Arylhydrazono derivatives may be prepared from 4-oxo-6,7,8,9-tetrahydro-4*H*- or 9-formyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine with aryldiazonium salts.³⁰⁷

9-Hydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines can also be prepared from 9-halo-,³⁰⁷ 9,9-dihalo-6,7,8,9-tetrahydro-,³²¹ and 9-hydroxy-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines³⁰⁷ by treatment with hydrazines.

Ethyl 6-methyl-9-hydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines was condensed with benzaldehyde to yield a mixture of tetrahydro and dihydropyrido[1,2-*a*]pyrimidines (**254** and **255**) and was acylated with benzoyl chloride.³⁰⁷



If the reaction of 9-halo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines and amines was carried out in the absence of air, the 9-amino-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines were isolated, which could be oxidized by air to the 6,7-dihydro analogs.³⁰⁸ The latter were directly prepared from 9,9-dihalo-4-oxo-6,7,8,9-tetrahydro-³²² or 9-hydroxy-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines³⁰⁸ with amines.

9-Hydroxy-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines can be prepared by hydrolysis of the corresponding 9-amines.³¹⁶

9-Hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines have been O-alkylated^{46,54,59,78,88,138,140} and O-acetylated.^{58,78} O-Acetylation of a 9-hydroxy-6,7-dihydro derivative has also been reported.³¹⁶

The 9-carboxy group of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was esterified and the ester was transformed to the amide. This amidation could not be carried out in the 1,6,7,8-tetrahydro series.⁵⁸ The 4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylic acids undergo spontaneous decarboxylation.^{58,319}

9-Benzyl and 9-methyl derivatives may be prepared by the alkylation of 4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylates.⁵⁸

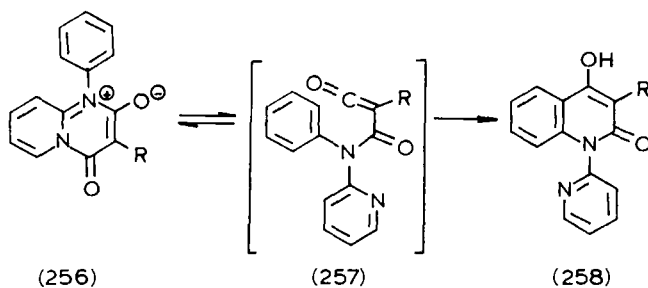
³²¹ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 883,219 [CA 94, 208894 (1981)].

³²² I. Hermecz, T. Breining, L. Vasvári-Debreczy, Á. Horváth, and J. Kőkösi, German Patent 3,017,560 [CA 95, 81007 (1981)].

10. Ring Transformations

On being heated with 5% aqueous alkali, 3-bromo-2-phenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was transformed to 2-phenylimidazo[1,2-*a*]pyridine, whereas the 2-methyl analog in 7% aqueous potassium hydroxide yielded a mixture of the 3-unsubstituted- and 3-carboxy-2-methylimidazo[1,2-*a*]pyridines. Under similar conditions, 3-bromo-2-chloro- and 3-bromo-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines decomposed to 2-aminopyridine.²⁹⁴

6-Substituted-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines of type **74** (6-*R* ≠ H) are transformed to 1,4-dihydro-4-oxo-1,8-naphthyridines on the action of heat.^{69,71,79,129,133,323-325} Ring transformation is facilitated by the nearly coplanar disposition of the 4-CO group and the 6-substituent of the pyrido[1,2-*a*]pyrimidines. The steric interaction of these groups is shown by the relatively long C-4—N-5 bond (e.g., 147 pm for ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, as determined by X-ray study³²⁶). The strain caused by this interaction is relieved when the C-4—N-5 bond cleaves. Ring transformation probably takes place via the reactive imino-ketene intermediate (**75**).¹³⁰



The pyrido[1,2-*a*]pyrimidines (**256**) undergo an essentially similar ring transformation, with the difference being that the ring closure of the intermediate iminoketene (**257**) takes place not to the C-3 atom of the pyridine ring but to the more reactive phenyl ring, and thus a quinoline derivative (**258**) is isolated.³²⁷

Reaction of the pyrido[1,2-*a*]pyrimidine (**259**) with acetylene derivatives leads to the quinolizines (**261**).¹²² Since the reaction is accompanied by

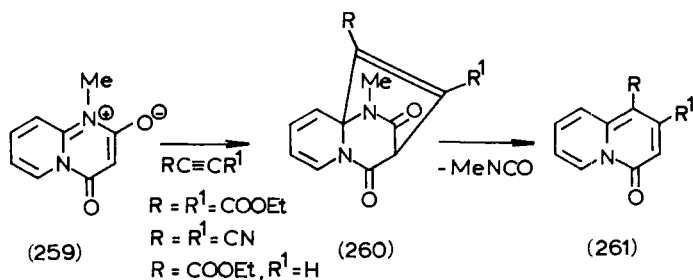
³²³ Z. Mészáros, G. Horváth, I. Hermecz, L. Vasvári-Debrecezy, Á. Horváth, Á. Dávid, V. Kovács-Mindler, and M. Csákvári-Pongor, French Demande 2,190,820 [*CA* **81**, 13477 (1974)].

³²⁴ CHINOIN Chem. Pharm. Works Ltd., Belgian Patent 824,491 [*CA* **84**, 31119 (1976)].

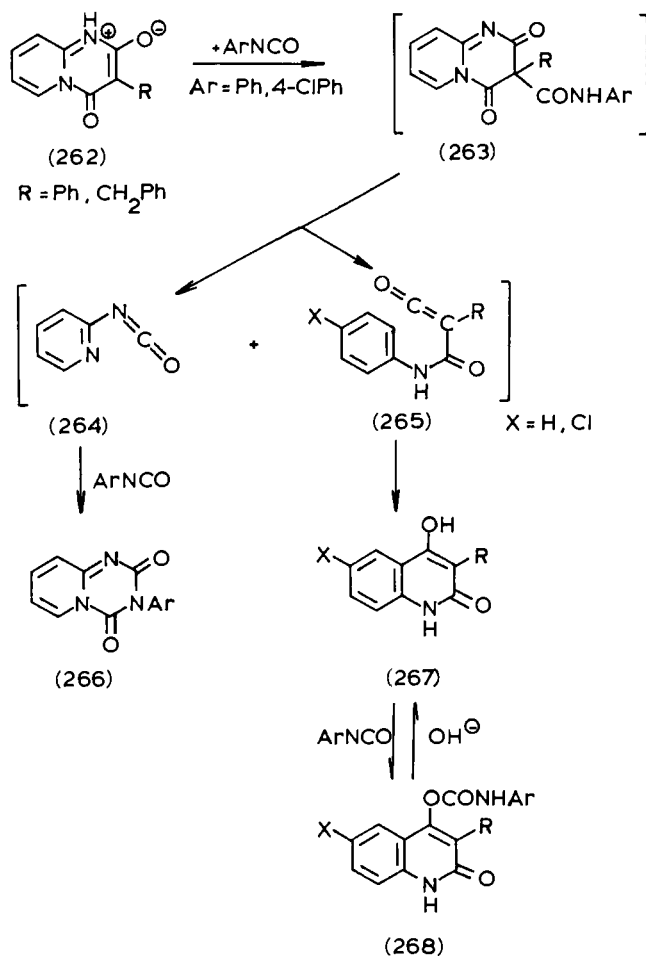
³²⁵ CHINOIN Chem. Pharm. Works Ltd., Netherlands Patent Appl. 7,603,192 [*CA* **87**, 53250 (1977)].

³²⁶ K. Sasvári, J. Csonka-Horvai, and K. Simon, *Acta Crystallogr., Sect. B* **B28**, 2405 (1972).

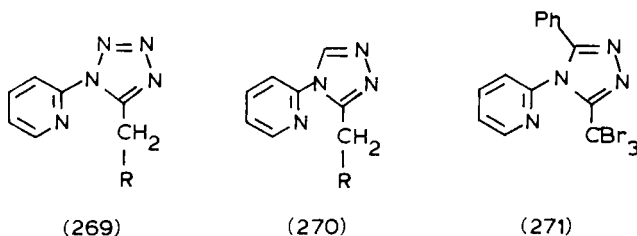
³²⁷ T. Kappe and W. Lube, *Chem. Ber.* **112**, 3424 (1979).



methyl isocyanate formation, it has been assumed to proceed via the intermediate (260).



On prolonged reaction with aryl isocyanates, the pyrido[1,2-*a*]pyrimidines (**262**) give pyrido[1,2-*a*]-s-triazines (**266**) in poor yield.³²⁸ The suggested pathway is the addition of the aryl isocyanate to form the 3,3-disubstituted product (**263**), which eliminates the ketene (**265**); the residual part of the molecule (**264**) reacts with an additional mol of aryl isocyanate to give **266**. The ketene (**265**) forms the quinoline (**267**), by ring closure, which gives **268** by aryl isocyanate addition. The quinoline (**267**: R = CH₂Ph, X = H) could be isolated.



When heated with bases, the 2-azidopyrido[1,2-*a*]pyrimidine (**102**) yields pyridyltetrazoles (**269**: R = CONR¹R²). This reaction is initiated by nucleophilic addition of the base to the carbonyl group; it is followed by ring opening between the C-4 and N-5 atoms and formation of the tetrazole ring involving the azido group and the N-1 atom of the starting pyrido-pyrimidine.^{166,291}

When the base was diethylamine, the pyrido[1,2-*a*]pyrimidine (**221**: R = R¹, R² = H) was formed with the tetrazole (**269**: R = CONEt₂). The ring transformation also took place as a result of photocatalysis.²⁹¹ When the azido compound (**102**) was heated in ethanolic hydrogen chloride for 1.5 h, the tetrazolylacetic acid (**269**: R = COOH) and its ethyl ester were obtained, while on prolonged treatment the methyl derivative (**269**: R = H) was the product.¹⁶⁶

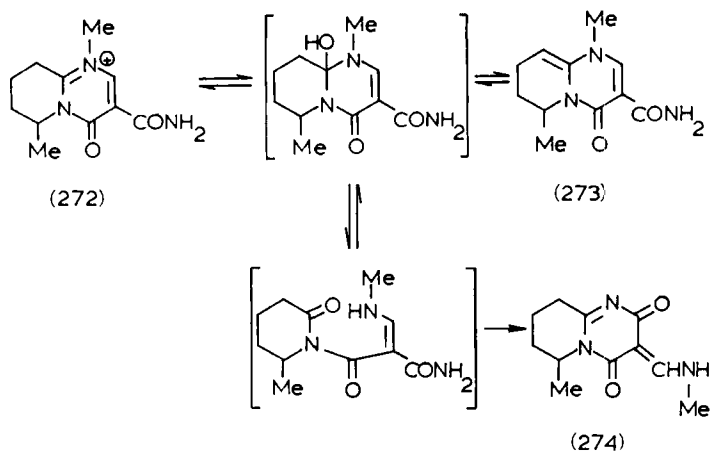
Heating of 2-formylhydrazono-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine in polyphosphoric acid led to a 2:1 mixture of the pyridyltriazoles (**270**: R = COOH and H).¹⁶⁶

Condensation of 2-hydrazino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines with benzaldehyde, followed by treatment with bromine in acetic acid, afforded the pyridyltriazole (**271**).¹⁶⁶

Under basic conditions ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates underwent transformation to 4-oxo-1,4,5,6,7,8-hexahydro-1,8-naphthyridines.^{133,329}

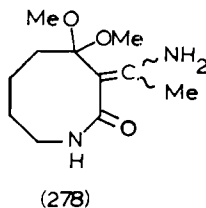
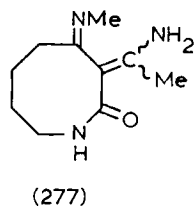
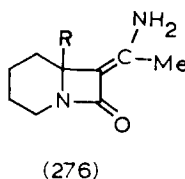
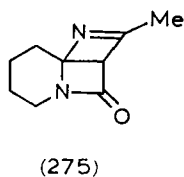
³²⁸ W. Stadlbauer, O. Schmut, and T. Kappe, *Monatsh. Chem.* **108**, 367 (1977).

³²⁹ I. Hermecz and Z. Mészáros, *Heterocycles* **12**, 1407 (1979).



When the quaternary salt (272) or the 1,6,7,8-tetrahydro-pyrido[1,2-*a*]-pyrimidine (273) was heated in sodium hydrogen carbonate solution, the pyrido[1,2-*a*]pyrimidine (274) was formed. This transformation proceeded via addition of water to the C-9a=N-1 or the C-9=C-9a double bond, followed by opening of the pyrimidine ring and finally by recyclization through condensation between the carbamoyl group and the oxo function of the piperidine ring.³³⁰

Nagata *et al.* studied the photochemical transformation of 2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones^{186,331-334} and iso-



³³⁰ I. Hermecz, J. Engler, Z. Mészáros, and G. Tóth, *Tetrahedron Lett.*, 1337 (1979).

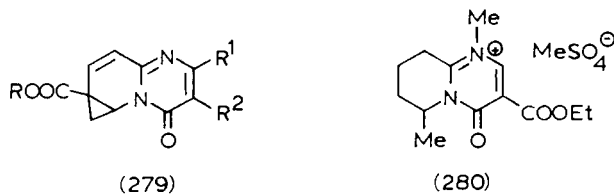
³³¹ T. Yamazaki, M. Nagata, S. Hirokami, Y. Hirai, and T. Date, *Heterocycles* **9**, 505 (1978).

³³² S. Hirokami, Y. Hirai, M. Nagata, T. Yamazaki, and T. Date, *J. Org. Chem.* **44**, 2083 (1979).

lated a number of products, including **276–278**. They demonstrated that in the first step a Dewar-type pyrimidinone, **275** could be detected by ^{13}C NMR in CDCl_3 at -20°C . Formation of the Dewar-type product from the cisoid diene system in the excited state by electrocyclic disrotatory ring closure is a symmetry-allowed process.

11. Miscellaneous Reactions

The carbamoyl group in position 7 could be transformed by phosphoryl chloride to a nitrile group.⁷⁹ 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylic acids were esterified by various methods and the esters cyclized to the tricyclic compounds (**279**) by treatment with trimethylsulfoxonium iodide in dimethyl sulfoxide in the presence of sodium hydride.⁶⁰



Reactions of the 8-methyl group of unsaturated pyrido[1,2-*a*]pyrimidines are discussed in Sections III.C.5 and III.C.6.

1-Alkyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium salts may be converted to 1-alkyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines by treatment with bases.^{75,133,257,271,311} This transformation can be reversed by acids.

Crystalline complexes were formed from ethyl 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and zinc chloride⁷⁵ and from the quaternary salt (**280**) and mercuric potassium iodide.^{335–337}

Optical resolution of 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid was carried out with the antipodes of

³³³ Y. Hirai, T. Yamazaki, S. Hirokami, and M. Nagata, *Tetrahedron Lett.* **21**, 3067 (1980).

³³⁴ S. Hirokami, T. Takahashi, M. Nagata, Y. Hirai, and T. Yamazaki, *J. Org. Chem.* **46**, 1769 (1981).

³³⁵ G. Szász, Z. Mészáros, A. Gergely, and P. Hardi, *Magy. Kem. Foly.* **80**, 314 (1974) [*CA* **82**, 8194 (1975)].

³³⁶ G. Szász, Á. Dávid, Z. Mészáros, and S. Ignáth, *Acta Pharm. Hung.* **47**, 120 (1977) [*CA* **87**, 189348 (1977)].

³³⁷ G. Szász, M. Medgyaszay, and L. Csordás, *Magy. Kem. Foly.* **85**, 289 (1979) [*CA* **91**, 202514 (1979)].

1-phenylethylamine²⁷⁹ or *threo*-1-(*p*-nitrophenyl)-2-aminopropane-1,3-diol.^{133,338,339} The optically active carboxylic acid in turn was utilized for the resolution of racemic propanediol.^{339,340}

D. 3,4-DIHYDRO-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

Reduction of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine (**135**) with sodium in ethanol¹⁹¹ or by catalytic hydrogenation over platinum(IV) oxide afforded the perhydropyrido[1,2-*a*]pyrimidine (**282**).¹⁹²

3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidines were quaternized with alkyl halides or benzyl chloride.^{188,189,193}

The hydroxy group of 3-hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine was acylated with acid chlorides in pyridine³⁴¹ and exchanged for chlorine by treatment with thionyl chloride.¹⁹⁰ The resulting chloro derivative (**131**: mp = 46.5–47°C) was transformed on standing to a compound containing ionic chlorine (mp = 193°C). The structure of the latter remained unclarified.¹⁹⁰

E. 2-Oxo-3,4-DIHYDRO-2*H*- AND 4-Oxo-2,3-DIHYDRO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

On the action of water^{200,204,205} or ammonia,²⁰⁰ 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines (**142**) undergo a facile ring opening. The betaine-type products (**143**) can be recycled to the parent pyridopyrimidines by heating with acids. Treatment with alkalis leads to 2-aminopyrimidines.^{200,205,208}

Lappin obtained the propionates (**144**) by heating the 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines (**142**: R = H, Me) in methanol.¹⁹⁷

When the pyrido[1,2-*a*]pyrimidines (**158**: R = Me) are heated in chloroform they are converted by cleavage of the C-4—N-5 bond to the amides (**159**: R¹ = Me).²¹⁸ On standing in methanol at room temperature, the pyrido[1,2-*a*]pyrimidine (**158**: R¹ = Ph) gives a mixture of the amide

³³⁸ E. Fogassy, M. Ács, and I. Hermecz, *Period. Polytech., Chem. Eng.* **20**, 263 (1976) [*CA* **87**, 84930 (1977)].

³³⁹ E. Fogassy, Z. Mészáros, I. Hermecz, L. Vasvári-Debczy, Á. Horváth, and M. Ács, British Patent 1,494,725 [*CA* **88**, 62410 (1978)].

³⁴⁰ E. Fogassy, M. Ács, I. Hermecz, and I. Máthé, *Period. Polytech., Chem. Eng.* **21**, 229 (1977) [*CA* **88**, 50404 (1978)].

³⁴¹ C. H. Tilford, M. G. Van Campen, and R. S. Shelton, *J. Am. Chem. Soc.* **69**, 2902 (1947).

(**159**: R¹ = Ph) and the pyrido[1,2-*a*]pyrimidine (**160**: R¹ = Ph)²¹⁷ (see Section II,E).

The pyrimidine ring of 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines is also susceptible to ring opening on the action of bases.^{205,215}

Hydrogenation of 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines over platinum(IV) oxide in ethanol yielded the 2-oxoperhydro derivatives.^{200,217} The oxo group of the latter was eliminated by reduction with lithium aluminum hydride.^{192,342}

3-Hydroxy-2-oxo-3,4-dihydropyrido[1,2-*a*]pyrimidine was *O*-acetylated with acetic anhydride and dehydrated to 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine (**18**) with phosphorus pentoxide.²⁰⁰

Bromination of the 7-bromo- and 7-chloro-2-oxo-3,4-dihydropyrido[1,2-*a*]pyrimidines and the 7-chloro-4-oxo-2,3-dihydropyrido[1,2-*a*]pyrimidines with bromine was unsuccessful, yielding only the hydrobromide salts of the starting materials.²⁰⁵

F. REACTIONS OF MISCELLANEOUS PYRIDO[1,2-*a*]PYRIMIDINES

3-Acetyl-2-phenyl-4-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidine was oxidized with chloranil to the 4-oxo compound.¹⁶⁸

The 6-oxopyrido[1,2-*a*]pyrimidine remained unchanged on catalytic hydrogenation (PtO₂, Raney nickel) but decomposed when treated with lithium aluminum hydride.²⁵⁵ The oxo group of the 6-oxo-9*a*-phenylpyrido[1,2-*a*]pyrimidine (**179**) was reduced with lithium aluminum hydride.^{230,232} On reduction with sodium borohydride, the 2-phenylpyrido[1,2-*a*]pyrimidine (**184**) gave the piperidine derivative (**182**).^{240,241} The 6-oxoperhydropyrido[1,2-*a*]pyrimidines were acylated at the N-1 atom with dichloroacetyl chloride.³⁴³

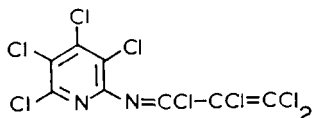
Perhydropyrido[1,2-*a*]pyrimidine was oxidized with the mercuric acetate-EDTA complex. When the reaction mixture was treated with potassium carbonate, 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was obtained, whereas on work-up with 20% sodium hydroxide the product was 1-(3-aminopropyl)-2-oxopiperidine.³⁴⁴

³⁴² E. E. Mikhлина, A. D. Yanina, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin.*, 547 (1969) [*CA* **71**, 124366 (1969)].

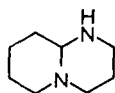
³⁴³ W. Rohr, H. Hansen, P. Plath, and B. Wuerzer, German Patent 2,948,535 [*CA* **95**, 150697 (1981)].

³⁴⁴ H. Möhrle and C. M. Seidel, *Arch. Pharm. (Weinheim. Ger.)* **309**, 471 (1976).

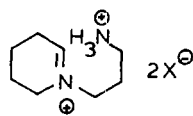
Oxidation of 2-phenyl-1-methylperhydropyrido[1,2-*a*]pyrimidine with the mercuric acetate–EDTA complex in 15% acetic acid yielded 1-[(3-phenyl-3-methylamino)propyl]-2-oxopiperidine.²⁴¹



(281)



(282)



(283)

Chlorination of the pyrido[1,2-*a*]pyrimidine (**189**) yielded a perchlorinated pyridine derivative (**281**).²⁴⁴ Perhydropyrido[1,2-*a*]pyrimidine (**282**) is sensitive towards acids, with ring cleavage to **283** taking place.¹⁹¹ The latter can be recycled by alkali.¹⁹² Hydrogenation in concentrated hydrochloric acid over platinum(IV) oxide yields 1-(3-aminopropyl)piperidine.^{192,342} Hydrogenation over Raney nickel in the presence of acetaldehyde leads to 1-ethylperhydropyrido[1,2-*a*]pyrimidine.²³⁷

Perhydropyrido[1,2-*a*]pyrimidine (**282**) can be converted in an acetic anhydride–formic acid mixture to the 1-formyl derivative, and the 1-formyl group can be reduced to the methyl group with lithium aluminum hydride.³⁴² Treatment with ethylene oxide in the presence of sodium hydroxide leads to the 1-(2-hydroxyethyl) derivative,³⁴² and heating with diethylaminoethyl chloride in acetone in the presence of triethylamine gives the 1-(2-diethylaminoethyl)perhydropyrido[1,2-*a*]pyrimidine.^{276,277}

3,4,6,7,8,9-Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was quaternized with alkyl halides.³⁴⁵

In aqueous solution the 4-oxo-2,3,6,7,8,9-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine (**198**; R = H) was transformed into the propionic acid derivative (**197**; R = H) and the cyclic diamide (**195**).^{249,250}

IV. Physicochemical Properties of Pyrido[1,2-*a*]pyrimidines

This section gives references where physicochemical data for pyrido[1,2-*a*]pyrimidines are available; it also lists the most characteristic physicochemical properties of these compounds.

For the pyrido[1,2-*a*]pyrimidinium salts UV,^{2-4,6,8,9,13,14,17,252,346} fluorescence,³⁴⁶ IR,^{2,5,17} ¹H NMR,^{2-5,9,13,17} and mass spectral^{2,17} data are available.

³⁴⁵ D. J. Ellis and D. Rammler, U.S. Patent 3,652,564 [CA **76**, 153771 (1972)].

³⁴⁶ G. W. Fischer, *J. Prakt. Chem.* **316**, 875 (1974).

Similarly to those of quinoline, isoquinoline and quinolizinium salts, the UV spectra of the pyrido[1,2-*a*]pyrimidinium salts, show absorption in three regions: (1) 290–370 nm (this region may show fine structure), (2) 270–280 nm, and (3) 225–230 nm (the most intense region).^{6,14}

In the IR spectra of the pyrido[1,2-*a*]pyrimidinium salts, the band at 1630–1650 cm^{-1} may be assigned to the $\text{C}=\text{N}^+$ double bond.^{2,5}

The 2- and 4-substituted pyrido[1,2-*a*]pyrimidinium salts may be distinguished by ^1H -NMR spectroscopy. In the 2-substituted derivatives the coupling constant $J_{3,4} = 6.9\text{--}7.6$ Hz, whereas in the 4-substituted compounds $J_{2,3} = 4.0\text{--}5.0$ Hz.^{3,5,13} In the isomeric methyl compounds the signal for the CH_3 -2 generally appears at 2.50–3.00 ppm and that for the 4- CH_3 at 2.75–3.25 ppm.^{3–5,13}

The electron density distribution and bond order of the individual bonds of the pyrido[1,2-*a*]pyrimidinium cation (**16**) have been calculated by the Hückel⁸ and the PPP³⁴⁷ methods.

As discussed in Sections II,B and C, the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines have often been incorrectly described as 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines^{34,38,92} or as 1,8-naphthyridines.^{33,81,128} These three types of compounds can be distinguished on the basis of their UV, NMR, and mass spectra.

The first comparison of the UV spectra of the 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines was made by Adams and Pachter.¹⁸ On the basis of their data corrected some erroneous assignments found in the literature.

By studying the UV spectra of 1,2- and 2,3-condensed pyrimidin-4-ones. Allen *et al.*³⁴⁸ established that the main absorption bands of the 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines fall into three regions (*a*, *b*, and *c*) and that the intensities of the absorption maxima and the molar extinction ratios (ϵ_c/ϵ_b) are characteristic for the isomeric compounds (see Table II).

Antaki concluded that the absorption band for the 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines in the range 300–400 nm can be ascribed to the 2-imino-1-substituted-1,2-dihydropyridine chromophore, and the band in the interval 250–270 nm to the $\text{C}=\text{C}-\text{C}=\text{O}$ chromophore of the molecules.^{29,87}

Adams and Pachter¹⁸ interpreted the higher melting point and better polar solubility of the 2-oxo-2*H* isomers in terms of the higher contribution of a zwitterionic mesomeric form to the structure.

³⁴⁷ V. Galasso, *Theor. Chim. Acta* **11**, 417 (1968).

³⁴⁸ C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allen, *J. Org. Chem.* **24**, 779 (1959).

TABLE II
ULTRAVIOLET ABSORPTION SPECTRA OF
ISOMERIC OXOPYRIDO[1,2-*a*]PYRIMIDINES

λ_{\max} (nm)	Molar extinction (ϵ)	
	2-oxo-2 <i>H</i> -	4-oxo-4 <i>H</i> -
<i>a</i> 210–230	high	high
<i>b</i> 250–270	high	medium
<i>c</i> 300–400	low	high
$\epsilon_c/\epsilon_b = \sim 1/3 > 1$		

In the IR spectra of the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines the CO stretching band is shifted by 20–30 cm⁻¹ to higher wavenumbers, as compared with the position for the 2-oxo-2*H* isomers.^{2,19}

The ¹H-NMR spectra of the isomeric 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines exhibit some characteristic differences. In the spectra of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, which are unsubstituted at position 6, the anisotropic effect of the adjacent carbonyl group causes the signal of the H-6 to be shifted downfield by about 1 ppm as compared with the corresponding signal for the 2-oxo-2*H* isomer.^{2,19,24,86}

4-Oxo-4*H*- and 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines unsubstituted in positions 2,3 and 3,4, respectively, can be distinguished on the basis of the coupling constants $J_{2,3} = 6.2$ Hz^{8,349} and $J_{3,4} = 7.1$ –7.7 Hz.^{8,23,349} In the 2-oxo-pyrido[1,2-*a*]pyrimidines a long-range coupling with $^4J \approx 0.1$ Hz can be observed between the H-4 and H-9 atoms.^{8,349}

As a consequence of complexing of the shift reagent Eu(fod)₃ with the 4-CO group of the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, the H-3 and H-6 signals suffer the most pronounced shifts.^{45,173}

Kato *et al.*¹⁹ compared the mass spectra of 2-methyl-4-oxo-4*H*- and 4-methyl-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines. Fragments at $m/e = 120$ and 92 appeared only in the spectrum of the 2-oxo isomer. In the spectrum of the 4-oxo isomer the peak at $m/e = 105$ corresponds to a single fragment of composition C₆H₅N₂, whereas for the 2-oxo isomer, it is a mixture of two fragments, C₆H₅N₂ and C₇H₇N.

Comparison of the spectral data on the isomeric 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines and 4-oxo-1,4-dihydro-1,8-naphthyridines revealed that in the UV spectrum the highest wavelength maximum is generally situated

³⁴⁹ A. Pollak, B. Stanovnik, and M. Tisler, *Chimica* **24**, 418 1970 [*CA* **74**, 125625 (1971)].

above 340 nm for the pyridopyrimidines and below 340 nm for naphthyridines. In the IR spectra (in KBr) the carbonyl stretching band is in the range 1670–1705 cm^{-1} for the pyridopyrimidines and in the range 1615–1680 cm^{-1} for the naphthyridines.^{79,350} The mass spectra of the isomeric compounds display characteristic differences.³⁵¹

The structure of the reaction product of 2-aminopyridine and diethyl malonate, described by Chichibabin as 2,4-dioxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine,⁹⁶ was first questioned by Snyder and Robison²⁵³ on the basis of the high melting point and poor solubility of the compound. They suggested the tautomeric 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine structure. The problem was solved by Katritzky and Waring²⁷³ who compared the UV spectrum of the product with that of fixed tautomers and found that the product may best be described as *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxide (**63**). Because of the chemical behavior of these compounds, however, the contribution of other mesomeric forms to the structure has also been considered.¹²² Thus, PPP–SCF quantum chemical calculations suggest that 1,4-dipolar cycloadditions to the C-3 and C-9a atoms are to be expected.³⁵² This type of reaction does in fact occur (see Section III,C,10). Katritzky and Waring²⁷³ estimated the ratio of the mesomeric betaine (**63**; R = H) and the 2-hydroxy-4-oxo tautomers to be about 20:1.

Urban *et al.*¹¹² compared the UV, IR, and ¹H-NMR spectra of the pyrido[1,2-*a*]pyrimidines (**63**) with those of their 1-alkyl and 2-alkoxy derivatives.

The UV,^{117,350,353,354} luminescence,³⁵⁵ ESCA,³⁵⁶ IR,^{117,354,357} ¹H-NMR,^{117,358} and ¹³C-NMR³⁵⁸ spectral behavior of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines and their tetrahydro and hexahydro derivatives is well documented.

³⁵⁰ G. Horváth, M. Csákvári, Á. Dávid, P. Dvortsák, and Z. Mészáros, *Proc. Conf. Appl. Phys. Chem.*, 2nd., 1971, 425 (1971) [*CA* **76**, 71619 (1972)].

³⁵¹ J. Tamás, G. Bujtás, J. Hollos, and M. Bihari, *Kem. Kozl.* **46**, 504 (1976) [*CA* **87**, 67472 (1977)].

³⁵² R. A. Coburn, R. A. Carapellotti, and R. A. Glennon, *J. Heterocycl. Chem.* **10**, 479 (1973).

³⁵³ G. Horváth, I. Á. Kiss, Z. Mészáros, and I. Hermecz, *Acta Chim. Acad. Sci. Hung.* **83**, 15 (1974) [*CA* **82**, 30534 (1975)].

³⁵⁴ F. Billes, M. Kubinyi, A. Martin, and É. Moharos, *Period. Polytech., Chem. Engin.* **23**, 169 (1979) [*CA* **93**, 113394 (1980)].

³⁵⁵ I. Szilágyi, J. Szöke, F. Engard, and G. Horváth, *Colloq. Spectrosc. Int. [Proc.]*, 18th, 1975 Vol. 3, 739 (1975) [*CA* **88**, 5705 (1978)].

³⁵⁶ R. Szargan and T. Kappe, *Z. Chem.* **20**, 441 (1980) [*CA* **94**, 191090 (1981)].

³⁵⁷ G. Horváth, M. Pongor-Csákvári, I. Á. Kiss, G. Fogarasi, and T. Pulay, *Tetrahedron* **33**, 2293 (1977).

³⁵⁸ G. Tóth, I. Hermecz, and Z. Mészáros, *J. Heterocycl. Chem.* **16**, 1181 (1979).

¹H-NMR studies have demonstrated that, depending on the substituents and solvent, the 9-alkoxycarbonyl, 9-carbamoyl, or 9-formyl derivatives of 4-oxo-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines exist as 6,7,8,9- and/or 1,6,7,8-tetrahydro tautomers.^{58,178,181,319,320} In chloroform the 3,4,6,7,8,9-hexahydropyridopyrimidine (**274**) is present predominantly in the **274** form, while in DMSO-*d*₆ the latter structure gives a mixture with the tautomeric 1,3,4,6,7,8-hexahydro form.³³⁰

To aid in the interpretation of the spectral properties and reactivities of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, PPP,^{359–361} CNDO/2,¹⁴⁸ and CNDO/S-CI³⁶² calculations have been carried out.

The mass spectral properties of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines with various degrees of saturation were studied by Tamás *et al.*^{351,363}

The structures of several 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines have been studied by X-ray diffraction.^{45,326,337,364–370}

Reports have been published on the chromatographic^{305,371–376} and polarographic³⁷⁷ behavior, the partition coefficients,³⁷⁸ and the analytical

³⁵⁹ G. Náray-Szabó, E. Dudar, and G. Horváth, *Proc. Conf. Appl. Phys. Chem.*, 2nd. 1971, 409 (1971) [*CA* **76**, 71595 (1972)].

³⁶⁰ G. Náray-Szabó, E. Dudar, and G. Horváth, *Acta Chim. Acad. Sci. Hung.* **74**, 281 (1972) [*CA* **78**, 42664 (1973)].

³⁶¹ E. Dudar, I. Á. Kiss, and G. Horváth, *Acta Chim. Acad. Sci. Hung.* **78**, 253 (1973) [*CA* **80**, 36601 (1974)].

³⁶² P. Surján, *Kem. Kozl.* **54**, 234 (1980) [*CA* **95**, 168247 (1981)].

³⁶³ J. Tamás, G. Bujtás, K. Ujszászi, and Z. Mészáros, *Proc. Int. Symp. Gas Chromatogr. Mass Spectrom.*, 1972, 189 (1972) [*CA* **78**, 110037 (1973)].

³⁶⁴ K. Simon and K. Sasvári, in *Proc. Conf. Appl. Phys. Chem.*, 2nd., 1971, 339 (1971) [*CA* **76**, 91321 (1972)].

³⁶⁵ K. Simon and K. Sasvári, *Cryst. Struct. Commun.* **1**, 419 (1972).

³⁶⁶ K. Sasvári and K. Simon, *Acta Crystallogr., Sect. B* **29**, 1245 (1973).

³⁶⁷ K. Simon and K. Sasvári, *Acta Crystallogr., Sect. B* **31**, 1695 (1975).

³⁶⁸ K. Simon, Z. Mészáros, and K. Sasvári, *Acta Crystallogr., Sect. B* **B31**, 1702 (1975).

³⁶⁹ K. Sasvári, K. Simon, Z. Mészáros, G. Horváth, and P. Dvortsák, *Cryst. Struct. Commun.* **5**, 611 (1976).

³⁷⁰ K. Simon, *God, Jugosl. Cent. Kristallogr.* **15**, 87 (1980).

³⁷¹ G. Szász, Z. Mészáros, Z. Ignáth, and G. Kovács, *J. Chromatogr.* **117**, 345 (1976).

³⁷² S. Bárány-Budvári, G. Szász, and S. Perneczky, *Magy. Kem. Foly.* **81**, 30 (1975) [*CA* **82**, 160638 (1975)].

³⁷³ O. Papp, G. Szász, and K. Valko, *J. Chromatogr.* **191**, 245 (1980).

³⁷⁴ G. Szász, M. Szász-Zacsó, Á. Csejtej, and B. Gasko, *Acta Pharm. Hung.* **49**, 271 (1979) [*CA* **92**, 153249 (1980)].

³⁷⁵ E. János, F. Darvas, O. Papp, K. Valko, and G. Szász, *J. Chromatogr.* **202**, 122 (1980).

³⁷⁶ O. Papp, G. Szász, K. Valkó, K. Hankó-Novák, I. Hermecz, and J. Kökösi, *Acta Pharm. Fenn.* **90**, 107 (1981). [*CA* **95**, 114544 (1981)].

³⁷⁷ M. Grofcsik, *Magy. Kem. Foly.* **76**, 354 (1970) [*CA* **73**, 126449 (1970)].

³⁷⁸ K. Hankó-Novák, G. Szász, O. Papp, J. Vámos, and I. Hermecz, *Acta Pharm. Hung.* **51**, 246 (1981). [*CA* **96**, 67938 (1982)].

determination³⁷⁹ of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, as well as on the conductivity of pyrido[1,2-*a*]pyrimidine complexes.^{335,336} Fewer data are to be found on the spectral (UV, IR, and ¹H-NMR) behavior of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines.^{192,194,380} UV,^{200,206,210,217,218} IR,^{199,202,204,217,218} ¹H-NMR,^{198,199,217,218} and mass spectral¹⁹⁹ data have been reported on 2-imino- and 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines.

The Bohlmann band appearing between 2650 and 2800 cm⁻¹ in the IR spectra indicated that the unsubstituted perhydropyrido[1,2-*a*]pyrimidines contain the two rings in trans annellation.^{238,276,277}

Quantum chemical calculations by means of the CNDO/2 and INDO methods were carried out for the 4-oxo compound (**198**; R = H), for the isomeric 6-oxo compound, and for the 9a-hydroxy-substituted perhydro derivative.³⁸¹

The following spectral data are also available: for 4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines—UV, IR, ¹H NMR, and MS²¹⁵; for 4-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidines—UV⁹, IR^{9,168}, and ¹H NMR^{9,168}; for 6-oxo-6*H*-pyrido[1,2-*a*]pyrimidines and their saturated derivatives—UV, IR and ¹H NMR^{219,222,225,230}; for 4-oxohexahydro-4*H*-pyrido[1,2-*a*]pyrimidines (**198**; R = H)—IR^{249,250} and MS²⁵¹; for 2-oxo-3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidines—IR^{241,242,342}; and for perhydropyrido[1,2-*a*]pyrimidines—IR,^{192,230,236,241,276,277} ¹HNMR,^{230,238,239} and MS.²³⁹

V. Applications of Pyrido[1,2-*a*]pyrimidines

Pyrido[1,2-*a*]pyrimidines are being increasingly subjected to study, primarily because of their valuable biological properties.

The following biological effects are mentioned in patents for 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines: CNS activity, including antipyretic, tranquilizer, sedative, analgesic and/or muscle relaxant effects,^{55,56,59,66,72,74,76,83,88,101,102,104,131,132,138,140,160,257,259,261,262,264,269,270,272,279,280,382} as well as antiinflammatory,^{131,132,142,143,257,261,270,272,279,311} antiallergic,^{155,307,308,310,321,322} hypotensive,^{57,66,83,140,262–264} coronary vasodilatory,²⁸¹ thrombocyte aggregation inhibitory,³¹¹ anti-atherosclerotic,²⁶⁶

³⁷⁹ A. Tóth, Á. Dávid, and G. Horváth, *Proc. Conf. Appl. Phys. Chem.*, 2nd., 1971, 417 (1971) [*CA* **76**, 90112 (1972)].

³⁸⁰ L. S. Povarov, *Khim. Geterotsikl. Soedin.*, 1694 (1979) [*CA* **92**, 110889 (1980)].

³⁸¹ J. Maranon, O. M. Sorarra, H. Grinberg, S. Lamdan, and C. H. Grazza, *Tetrahedron* **34**, 53 (1978).

³⁸² J. Knoll, S. Fürst, Z. Mészáros, G. Nagy, Á. Dávid, R. Bognár, S. Makleit, and G. Valovich, German Patent 2,461,349 [*CA* **83**, 197808 (1975)].

serotonin antagonistic,⁷⁰ insecticidal,^{108,179,180} and antibacterial and antimicrobial effects.^{59,78,88} Also, for 2-arylpyrido[1,2-*a*]pyrimidinium salts, a biocidal effect¹⁵ is mentioned. Penicillin and cephalosporin derivatives have been acylated with 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids.^{141,310,313} Some 6-oxo-pyrido[1,2-*a*]pyrimidines have been patented as CNS-active compounds (analgesics, sedatives,^{220,228,229,231} and anticonvulsants²²⁸), antiinflammatory agents,^{220,228,229,231,232} hypotensives and coronary vasodilators,²²³ agents reducing blood cholesterol and lipid levels,²²³ and herbicide antagonists.³⁴³ 3,4,6,7,8,9-Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidines and their quaternary salts have been found to exhibit antibacterial,^{234,345} blood sugar level reducing, thrombocyte aggregation inhibitory,²³⁵ diuretic, hypertensive, and antiphlogistic effects.²³⁴ Finally, 9a-phenylperhydropyrido[1,2-*a*]pyrimidines exhibit antiinflammatory effects.²³²

The first detailed paper in the field of the pharmacology of the pyrido[1,2-*a*]pyrimidines was a study on the histamine-liberating and nonspecific spasmolytic activity of 2-(2-dimethylaminoethyl)-3-(4-methoxyphenylmethyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine.³⁸³

Of the investigated 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, compound (**63**: R = H) was moderately active against solid tumors,³⁸⁴ whereas its 7-carboxy derivative showed a weak antiallergic activity in the PCA test.⁶³ The blood sugar level reducing activity of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-esters and their derivatives is about one-sixth of that of tolbutamide.¹³⁶

In conjunction with other bicyclic amidines, the indolamine *N*-methyl transferase inhibitory activities of 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidines have been studied.²⁴⁶ The analgetic and antiinflammatory activities of 6-oxopyrido[1,2-*a*]pyrimidines have been tested in comparison with those of phenylbutazone.^{221,222}

2-Amino-3-substituted-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines were tested for antihypertensive and nonspecific MAO inhibitory effects.^{260,385-388}

Fujita *et al.*⁴⁹ reported the testing of more than 140 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines for cardiovascular activity.

³⁸³ T. P. Pruss and J. Hidalgo, *J. Pharm. Sci.* **54**, 886 (1965).

³⁸⁴ T. Kato, H. Kimura, A. Wogai, T. Saski, M. Ohkuma, H. Shinoda, M. Kohno, and D. Mizumo, *J. Pharm. Soc. Jpn.* **97**, 676 (1977).

³⁸⁵ C. L. Kaul and R. S. Grewal, *Biochem. Pharmacol.* **21**, 303 (1972).

³⁸⁶ K. Magyar, É. Satory, Z. Mészáros, and J. Knoll, *Orvostudomány* **25**, 143 (1974) [*CA* **82**, 12080 (1975)].

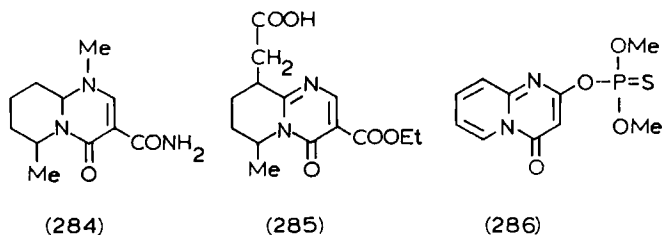
³⁸⁷ K. Magyar, É. Satory, Z. Mészáros, and J. Knoll, *Med. Biol.* **52**, 384 (1974).

³⁸⁸ É. Satory, Z. Mészáros, K. Magyar, and J. Knoll, *Congr. Hung. Pharmacol. Soc. [Proc.]* **2**, 43 (1974) (publ. 1976) [*CA* **88**, 115243 (1978)].

Knoll, Mészáros and others studied the structure–activity relationship of analgetic 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid derivatives.^{133,258,389,390} Following detailed investigations,^{391–436} derivatives

- ³⁸⁹ J. Knoll, Z. Mészáros, P. Szentmiklósi, and S. Fürst, *Orvostudomány* **20**, 361 (1969) [*CA* **73**, 23811 (1970)].
- ³⁹⁰ J. Knoll, Z. Mészáros, P. Szentmiklósi, and S. Fürst, *Arzneim.-Forsch.* **21**, 717 (1971).
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- ⁴⁰² K. Magyar and J. Knoll, *Acta Physiol. Acad. Sci. Hung.* **43**, 353 (1973) [*CA* **82**, 38412 (1975)].
- ⁴⁰³ S. Fürst and J. Knoll, in "Drug Interaction" (P. L. Morselli, S. Garattini, and S. N. Cohen, eds.), 277. Raven Press, New York, 1974.
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- ⁴¹⁵ J. Knoll, *Acta Physiol. Pharmacol. Bulg.* **3**, 9 (1977) [*CA* **89**, 52961 (1978)].
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- ⁴²⁰ G. Stampf, H. Juhász, E. Morzsányi, and L. Gyarmati, *Gyógyszereszet* **23**, 16 (1979) [*CA* **90**, 127484 (1979)].

273, **280**, and **284** were selected for further pharmacological examination. Pyrido[1,2-*a*]pyrimidine **284** has analgetic and antiinflammatory activity,^{431,432,435} and **273** also exhibits a thrombocyte aggregation inhibitory effect.



The 9-acetic acid derivative (**285**) was studied for its antiatherosclerotic effect.^{258,268,436–443} The 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**286**) was investigated in various tests for insecticidal effects.⁴⁴⁴

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Certain pyrido[1,2-*a*]pyrimidinium salts^{304,445} and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine derivatives^{109,278,298,299,303,446-450} have been patented as dyes sensitizing photographic silver halide emulsions and photoconducting layers. The 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines can also be used as optical sensitizers in the preparation of photosensitive polymers,¹⁴⁴ and as photo-degradation accelerators in polyolefins.⁴⁵¹ 2-Oxo-2*H*-pyrido[1,2-*a*]pyrimidines and 3,4-dihydro[1,2-*a*]pyrimidines and 3,4-dihydro derivatives are useful as posthardening degradation inhibitors in photographic materials.⁴⁵² 3,4-Dihydro-2*H*- and 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines have been patented as brightening agents for use in electrolytic galvanizing baths.⁴⁵³ 3-Hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines are used as stabilizers for polychloroprene rubber⁴⁵⁴ and as leather adhesives.⁴⁵⁵ 7-Bromo-4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidinium bromide has been patented as a stabilizer in the preparation of unsaturated polyester compositions,⁴⁵⁶ and metal complexes of pyrido[1,2-*a*]pyrimidines have been patented as dyes for polyamide and wool fibers.⁴⁵⁷ 3,4,6,7,8,9-Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine is applied as a catalyst in the preparation of polyarylene ether⁴⁵⁸ and polyurethanes⁴⁵⁹ and is also used in organic syntheses as a basic catalyst promoting dehydrohalogenation.²⁴⁵

⁴⁴¹ P. Szentmiklósi, S. Marton, M. Kovács, and L. Gyarmati, *Pharmazie* **34**, 551 (1979) [*CA* **92**, 104031 (1980)].

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⁴⁵⁶ E. W. Meyer and J. G. Klein, U.S. Patent 2,846,411 [*CA* **52**, 21238 (1958)].

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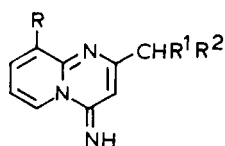
⁴⁵⁸ H. Wieden and U. Bahr, British Patent 1,134,613 [*CA* **70**, 29589 (1969)].

⁴⁵⁹ L. Jourguin and E. DuPrez, German Patent 2,710,901 [*CA* **87**, 202348 (1977)].

2-Oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines are neutral or slightly basic acid binders in the preparation of esters, amides, lactones, ethers, and amines.⁴⁶⁰⁻⁴⁶⁵

VI. Appendix

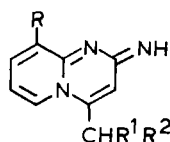
Landor and co-workers⁴⁶⁶ prepared the 2-imino- and/or 4-iminopyrido-[1,2-*a*]pyrimidines (**287** and **288**) from 2-aminopyridines with 4-alkylallenyl nitriles. The products were characterized via their UV spectra.



R = H, NH₂; R¹ = Me, Et;

R² = Et, Pr

(**287**)

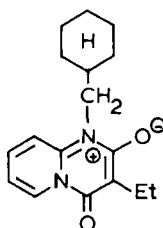


R = H, OH; R¹ = Me, Et, Pr;

R² = H, Me, Et

(**288**)

The pyrido[1,2-*a*]pyrimidine (**289**), prepared from 2-cyclohexylmethylaminopyridine and bis(2,4,6-trichlorophenyl) malonate at 160°C, exhibits phosphodiesterase inhibitory activity.⁴⁶⁷



(**289**)

⁴⁶⁰ M. Mukoyama and S. Kobayashi, Japan Kokai 78/02,403 [*CA* **88**, 190411 (1978)].

⁴⁶¹ T. Mukaiyama, H. Toda, and S. Kobayashi, *Chem. Lett.*, 13 (1976).

⁴⁶² T. Mukaiyama, Y. Aikawa, and S. Kobayashi, *Chem. Lett.*, 57 (1976).

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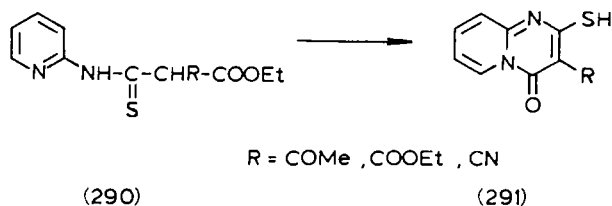
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⁴⁶⁶ T. Z. Fomun, J. T. Mbafor, P. D. Landor, and S. R. Landor, *Tetrahedron* **22**, 4127 (1981).

⁴⁶⁷ M. E. Rogers, R. A. Glennon, J. D. Smith, M. R. Boots, N. Nanavati, J. E. Maconanghey, D. Aut, and S. Thomas, *J. Med. Chem.* **24**, 1284 (1981).

Marchalin *et al.*⁴⁶⁸ have cyclized compounds **290** to pyridopyrimidines (**291**) thermally or in alcoholic solution in the presence of sodium ethoxide. The 2-mercapto group of compound **291** ($R = \text{COOEt}$) was alkylated with ethyl bromide. IR and MS data are given.



Tsuge and Noguchi⁴⁶⁹ prepared the 3-benzamido-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine and its methyl substituted derivatives from 2-aminopyridines and 2-phenyl-4-ethoxymethylene-5-oxazolone in boiling ethanol, without the isolation of the condensation products of type **94**. The pyrido-pyrimidine was formed from 2-amino-6-methylpyridine, but in a longer reaction period and in low percentage yield. Condensation product **94** was cyclized in ethanol or polyphosphoric acid or acetic acid. 3-Benzamido-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine was synthesized from 2-aminopyridine and the appropriate oxazolone derivative.

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Note Added in Proof

Much work on pyrido[1,2-*a*]pyrimidines that has been done recently has come to the attention of the authors since this chapter was submitted for

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publication. The work cannot be discussed here, but it was felt that the references should be provided.⁴⁷⁰⁻⁴⁹²

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